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RICHTER'S ORGANIC CHEMISTRY

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PUBLISHERS' NOTE

THIS Third Volume completes the translation of the English version of the eleventh edition of Richter's *Organic Chemistry* as edited by Professor R. Anschütz and Dr. H. Meerwein. In the original edition, the second and third volumes were issued together as a single book, but, to meet the urgent demand at the hands of the British and American publics, the second volume was issued in England and in the United States as soon as it could be got out.

Each of the three volumes contains its own Index. These have been prepared with great labour, and it is hoped will increase the utility of the volumes for rapid reference.

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A TEXT-BOOK
OF
ORGANIC CHEMISTRY

VOL. III. HETEROCYCLIC COMPOUNDS

THE carbocyclic substances treated in the preceding volume belong to the class of homocyclic compounds, which consist of rings of atoms of one and the same element. Apparently, very few elements are adapted to such a ring formation.*

However, substances are known in great number and complexity which are based upon ring-skeletons consisting of atoms of various elements. These bodies have been arranged under the designation "*heterocyclic compounds.*" It is true that a series of inorganic bodies† can be included in this category, but it is our purpose to consider only the "organo-inorganic"—*i.e.*, those ring-systems which are formed from carbon in union with other elements, the most important of which are oxygen, sulphur, but especially nitrogen. In many cases sulphur can be replaced by selenium, and there are some substances known in which phosphorus forms a ring with C-atoms. In diphenylene iodonium iodide a trivalent iodine atom takes part in forming a ring.‡

From the standpoint of organic chemistry, the basal element of these rings is carbon, and accordingly the members not produced by C-atoms are designated as *hetero-atoms,* and distinguished as *mono-*, *di-*, *tri-*, *tetra-*, etc., hetero-atomic rings, depending upon whether one, two, three, four, or more hetero-atoms have participated in their formation. To express the number of atoms constituting the entire ring, the rings are termed *three, four, five, six,* and *poly-membered rings.*

Many heterocyclic compounds have been discussed in the preceding chapters—for example, the polymeric modifications of aldehydes, like trioxymethylene and paraldehyde, the *cyclic ethers of the glycols and thioglycols,* like ethylene oxide, diethylene dioxide, diethylene disulphide; the *cyclic alkyleneimines*, like tetramethyleneimine or pyrrolidine, diethylenediimine, or piperazine; the *cyclic esters of oxy- and amino-acids*, like the lactides, the lactones, the lactams; the *cyclic derivatives of dibasic carboxylic acids*, like anhydrides, imides, alkylene esters, alkylenamides, etc. (see I. 497; ring-shaped compounds). These bodies attached themselves, as their names indicate, naturally to known classes of compounds with open chains. They can be readily obtained from substances with open chains, and be equally readily changed back into them. In the succeeding sections, however, a series of heterocyclic bodies will be described which manifest varying behaviour in so far that the rings upon which they are constructed cannot be resolved in a simple way. Such rings are rather nuclei to which side chains are attached, the products being related to the fundamental substances in the same way as that in which the aromatic substances are related to benzene. Usually, these substances, like benzene, contain unsaturated linkages.

---

* Nitrogen, mainly, in addition to carbon. The allotropic modifications of many elements are probably due to the formation of isocyclic rings—*e.g.*, that of oxygen in ozone, O_3.

† See Bischoff, "Handbuch der Stereochemie," p. 641.

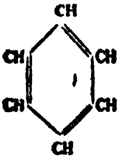
‡ Finally, rings are present in the salts of dicarboxylic acids, sulphocarbonic acids, disulphonic acids, glycols, etc., containing bi- and polyvalent metals. Members are formed by the metal atoms.

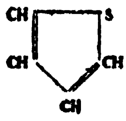
It has, therefore, been assumed that in these rings, as in benzene, there is a particular kind of linkage—" potential valences " (see Vol. II, p. 42 and B. **24**, 1761). These explain the stability of these bodies. If the potential valences are destroyed by the addition of hydrogen or some such substance, then saturated bodies result; these possess the " alicyclic character " (see Vol. II, p. 3), and so far as their decomposability is concerned, they in the main exhibit the character of the heterocyclic substances discussed after the fatty bodies. A real fundamental difference, however, between the two rings just described does not exist. Compounds were studied in connection with the lactones and dibasic anhydrides which offered great resistance to decomposition by water absorption, etc. (see I. 310, 371, 374). On the other hand, there are many bodies in which potential linkages are assumed, which are very easily decomposed by certain reagents—*e.g.*, pyrrole by hydroxylamine, yielding succinaldehyde-dioxime (I. 355), and glyoxaline by benzoyl chloride and sodium, forming dibenzoyldiaminoethylene, etc.

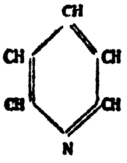
The heterocyclic rings containing five and six members are, like the analogous carbon rings, the most stable and important. They will be treated in this section. The tendency to the formation of six-membered rings is shown also in the processes of *polymerization;* formaldehyde, by the coalition of three molecules, becomes six-membered trioxymethylene; acetaldehyde becomes the six-membered paraldehyde, and the cyanogen compounds polymerize to derivatives of a six-membered ring, consisting of 3C- and 3N-atoms, etc. (compare Vol. II., p. 40). Three- and four-membered rings are usually formed with extreme difficulty, and are easily torn asunder. The seven-membered rings are not well known, and are also unstable. In a few compounds heterocyclic rings of eight or more members have to be assumed.

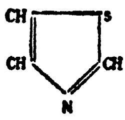
A theory of the type of A. von Baeyer's strain theory is made difficult by the varying nature of the hetero-atoms entering the ring. Certain facts can no doubt support some views regarding the spatial relations of many hetero-atoms.

Thiophene, with a ring of four CH-groups and one S-atom, very greatly resembles benzene, containing six CH-groups. Thiazole, consisting of three CH-groups, one N-atom, and one S-atom, similarly resembles pyridine, which has five CH-groups and one N-atom. It would therefore seem that a sulphur atom is capable of replacing the bivalent group —CH = CH— in the ring:

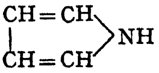

Benzene.

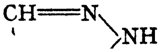

Thiophen.

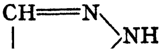

Pyridine.

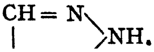

Thiazole.

It is an almost universal rule that an N-atom can replace a methine group in a ring without causing any essential loosening of the ring-union. If we suppose a methine group in benzene to be replaced by N, the product will be pyridine, which is about as stable a ring as we have in benzene. And if the methine groups in pyrrole be successively replaced by one, two, and three N-atoms, there also results a series of derivatives in which ring stability is very evident:


Pyrrole.


Pyrazole.


Pyrrodiazole.


Tetrazole.

A general review of the many heterocyclic ring systems can be obtained from two points of view. *Homologous series* are obtained by arranging together the rings with similar hetero-atoms according to the increasing number of C-members. The following series of rings have been deduced in this way:

(a) WITH AN O-MEMBER.

$:C{-}C:$ O	$:C{-}\ddot{C}{-}C:$ O	$:C{-}\ddot{C}{-}\ddot{C}{-}C:$ O	$:C{-}\ddot{C}{-}\ddot{C}{-}\ddot{C}{-}C:$ O
$H_2C{-}CH_2$ O Ethylene Oxide	$H_2C{-}CH_2{-}CH_2$ O Trimethylene Oxide	$H_2C{-}CH_2{-}CH_2{-}CH_2$ O Tetramethylene Oxide	$H_2C{-}CH_2{-}CH_2{-}CH_2{-}CH_2$ O Pentamethylene Oxide
—	—	$H_2C{-}CH_2{-}CH_2{-}CO$ O Butyrolactone	$H_2C{-}CH_2{-}CH_2{-}CH_2{-}CO$ O Valerolactone
—	—	$OC{-}CH_2{-}CH_2{-}CO$ O Succinic Anhydride	$OC{-}CH_2{-}CH_2{-}CH_2{-}CO$ O Glutaric Anhydride
—	—	$HC{=}CH{-}CH{=}CH$ O Furfurane	$HC{=}CH{-}CO{-}CH{=}CH$ O Pyrone

(*b*) WITH AN S-MEMBER.

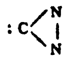
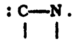
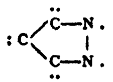
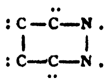
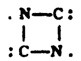
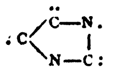
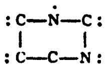
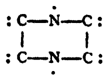
$:C-C:$ \S/	$:C-\ddot{C}-C:$ \S/	$:C-\ddot{C}-\ddot{C}-C:$ S	$:C-\ddot{C}-\ddot{C}-\ddot{C}-C:$ S
H_2C-CH_2 \S/ [Ethylene sulphide]	$H_2C-CH_2-CH_2$ S [Trimethylene sulphide]	$H_2C-CH_2-CH_2-CH_2$ S Tetramethylene sulphide	$H_2C-CH_2-CH_2-CH_2-CH_2$ S Pentamethylene sulphide
—	—	$CO-CH_2-CH_2-CO$ S Sulphosuccinyl	—
—	—	$CH=CH-CH=CH$ S Thiophene	$CH=CH-CH_2-C(CH_3)=CH$ S Methyl-penthiophene

(*c*) WITH ONE N-MEMBER.

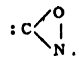
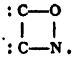
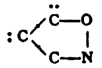
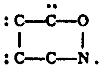
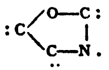
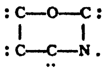
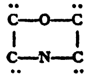
$:C-C:$ \N/	$:C-\ddot{C}-C:$ \N/	$:C-\ddot{C}-\ddot{C}-C:$ N	$:C-\ddot{C}-\ddot{C}-\ddot{C}-C:$ N
CH_2-CH_2 \NH/ Ethylene-imine	$CH_2-CH_2-CH_2$ NH Trimethylene-imine	$CH_2-CH_2-CH_2-CH_2$ NH Tetramethylene-imine Pyrrolidine	$CH_2-CH_2-CH_2-CH_2-CH_2$ NH Pentamethylene-imine Piperidine
—	—	$CH_2-CH_2-CH_2-CO$ NH Butyrolactam	$CH_2-CH_2-CH_2-CH_2-CO$ NH Valerolactam
$OC-CO$ \NH/ Oxal-imide (?)	$OC-CH_2-CO$ NH Malonimide (C. 1898 II., 858)	$OC-CH_2-CH_2-CO$ NH Succinimide	$OC-CH_2-CH_2-CH_2-CO$ NH Glutarimide
—	—	$CH=CH-CH=CH$ NH Pyrrole	$CH-CH=CH-CH=CH$ N Pyridine

Complication on account of isomerides arises in the case of rings having two hetero-atoms. These isomerides are occasioned by the varying positions of the hetero-atoms with reference to one another —*e.g.:*

RINGS WITH TWO N-MEMBERS.

 Hydrazi Compounds, Diazomethane	 Dimethylaziethane	 Pyrazole Group	 Pyridazine Group
—	 Ethidene Urea, Dicyan-compounds	 Glyoxaline Group, Cyclic Ureas	 Pyrimidine Group, Cyclic Ureas
—	—	—	 Pyrazine Group, Diethylene-diimide

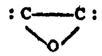
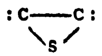
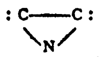
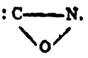
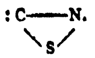
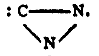
Rings with an O- and an N-Member.

 β-Benzaldoxime Ether	 Betaïne	 Isoxazole Group	 Orthoxazine Group
—	—	 Oxazole Group	 Metoxazine Group, Pentoxazoline
—	—	—	 Paroxazine Group

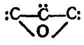
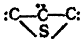
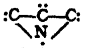
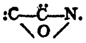
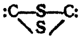
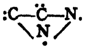
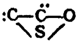
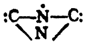
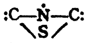
The three- and four-membered systems naturally disappear in the series of rings having three and four hetero-atoms. The branching of the series in consequence of position isomerides with the hetero-atoms becomes more frequent, so that the relations dependent upon homology frequently become obscure. In the monohetero-atomic rings also the homology usually appears solely in the case of the saturated (alicyclic) ring-systems, whereas the more important unsaturated systems, with more pronounced aromatic character, show at times very varying behaviour—*e.g.*, when in the homologous series with an N-member the group of the five-membered pyrrole comes into juxtaposition with that of the six-membered pyridine, although the representatives of these two groups manifest very great differences in their behaviour.

Hence it is more practical to group the ring-systems according to the number of members composing the ring. In this manner only systems of rings of approximately like stability will come together, and they will, therefore, very probably yield similar derivatives. Hence to rings of three atoms will be added such as have four, five, six, etc., members. Each of these groups will have subdivisions in accordance with the number of hetero-atoms, so that, for example, in the group of five-membered heterocyclic rings there will be discussed first the monohetero-atomic, then the di-, tri-, and tetrahetero-atomic systems. This might be called grouping according to *isologous series:*

Three-membered Heterocyclic Substances.

 Ethylene Oxide	 [Ethylene Sulphide]	 [Ethyleneimide] Oxalimide
 β-Benzaldoxime Ether	 Thialdolaniline	 Diazomethane, Hydrazi-compounds

FOUR-MEMBERED HETEROCYCLIC SUBSTANCES.

 Trimethylene oxide	 —	 Trimethylene-imine
 Betaïne	 Dithio-acetone	 Dimethylazi-ethane
—	 Thetin	 Alkylideneureas Dicyano Compounds (?)
—	 Alkylidene-ψ-thioureas	—

For Five-membered and Six-membered Heterocyclic Substances, see pp. 7, 8.

Just as indene, naphthalene, anthracene, etc., are derived from benzene, so numerous di- and polycyclic *condensed* nuclei are obtained from the heterocyclic rings that contain adjacent C-members. This is possible by the fact that the two adjacent C-members participate also in the formation of aromatic rings, like benzene, naphthalene, phenanthrene, etc. These condensed nuclei unite, as a rule, the properties of the carbocyclic with those of the heterocyclic ring. When definite names are not assigned them, as in the indol and quinoline groups, they are designated with the prefixes benzo- or phen-, dibenzo- or diphen,- naphtho-, etc., before the name of the heterocyclic ring.

Quite frequently substances having such condensed nuclei have the heterocyclic ring ruptured, and are then changed to ortho-substitution products of the carbon ring. Again, the heterocyclic ring shows itself more stable toward oxidizing agents, so that it is possible, by means of potassium permanganate, etc., to oxidize the condensed nuclei with destruction of the carbon ring and the production of ortho-dicarboxylic acids of the heterocyclic rings. Thus, acridine yields quinoline dicarboxylic acid, quinoline a pyridine-dicarboxylic acid, benzoglyoxaline a glyoxaline-dicarboxylic acid, benzotriazole a triazole-dicarboxylic acid, and phenazone a pyridine-tetracarboxylic acid, etc.

Both the simple and condensed heterocyclic compounds have, as a rule, been made by the internal condensation of suitable fatty or fatty-aromatic bodies having open chains. Very often the intermediate products, leading directly to the ring, cannot be isolated because of their great inclination to the ring formation; ortho-substitution products of benzene and naphthalene (Vol. II.) are especially well adapted for the production of condensed heterocyclic nuclei. They have afforded the starting-out material for the preparation of an immense number of substances belonging in this group.*

Many heterocyclic bodies also occur in technical and natural products. The large and important family of vegetable alkaloids belongs in the group of *pyridine* and the hydropyridines. *Pyridines* and *pyrroles* occur in coal-tar and bone-tar. *Thiophene* and *coumarone*

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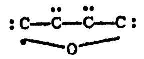
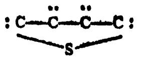
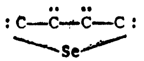
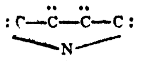
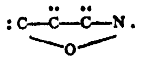
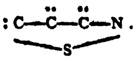
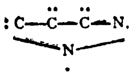
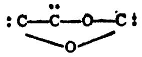
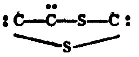
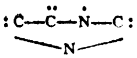
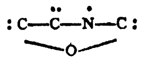
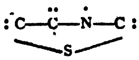
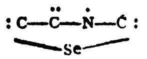
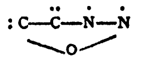
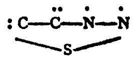
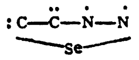
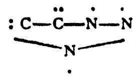
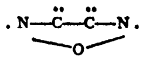
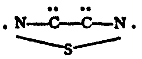
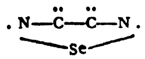
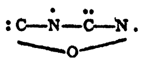
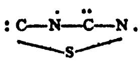
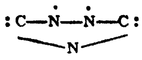
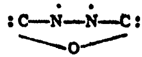
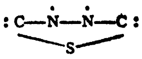
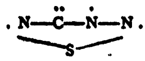
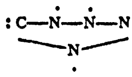
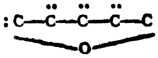
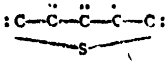
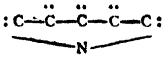
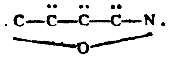
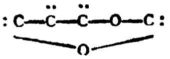
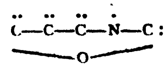
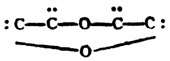
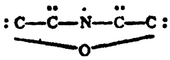
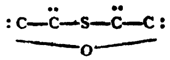
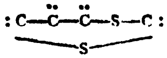
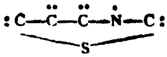
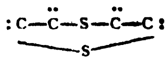
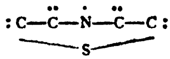
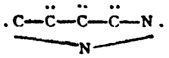
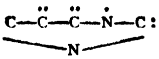
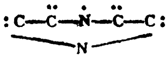
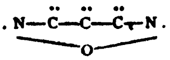
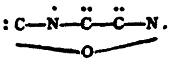
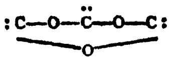
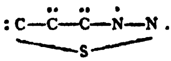
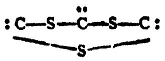
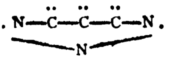
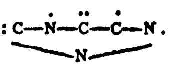
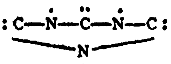
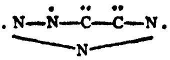
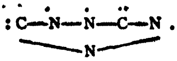
* Compare Kühling, "Stickstoffhaltige Orthocondensationsproducte," 1893.

Five-membered Heterocyclic Substances.

 *Furfurane*, γ-Lactones, Succinic Anhydride	 *Thiophene*, Sulphosuccinyl	 Selenophene	 *Pyrrol*, γ-Lactams, Succinimide
 *Isoxazole* Group	 Isobenzothiazole	—	 *Pyrazole* Group
 Cyclic Ethers and Esters of Glycol, Aldehyde, Carbonic Acid, and Oxalic Acid	 Ethidene-ethylene Disulphide	—	
			 *Glyoxaline* Group, Cyclic Ureas
 *Oxazole* Group	 *Thiazole* Group	 Selenazole Group	
 Diazo-oxides	 Diazosulphides	 Diazoselenide	 *Osotriazole* Group.
 Furazane Group	 Piazthioles	 Piaselenoles	
 Azoximes	 Azosulphimes	—	 *Triazole* Group
 *Oxybiazole* Group	 *Thiobiazole* Group	—	
—	 Triazsulpholes	—	 *Tetrazole* Group

are also present in coal-tar. *Furfural* and other derivatives of furan have been found in the tar from wood. The important vegetable dye, ***indigo***, and its allied bodies, are derivatives of indole. Many heterocyclic bodies prepared synthetically have been manufactured

SIX-MEMBERED HETEROCYCLIC SUBSTANCES.

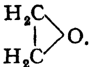
 Pentamethylene Oxide, δ-Lactones, Glutaric Acid Anhydride. *Pyrone* Group.	 *Penthiophene* Group	 Pentamethylene-imide (Piperidine). δ-Lactams, Glutarimide. *Pyridin* Group.
 Carboxyl-oxime Anhydrides  Cyclic Ethers and Esters of Trimethylene Glycol, Aldehyde, Carbonic Acid, Malonic Acid, etc.  *Pentoxazolin* Group  Diethylene Oxide, Cyclic Anhydrides of α-Oxyacids  *Paroxazin* Group  Thio-diglycollic Anhydride	—   *Penthiazoline* Group  Diethylene Disulphide  *Parathiazin* Group	 *Pyridazin* Group  *Pyrimidin* Group  *Pyrazin* Group
 Azoxazin Derivatives  Benzenylamidoxime Acetic Anhydride  Polymeric Aldehyde	 Diazothin Derivatives  Trithioaldehyde	 *Osotriazine* Derivatives  Unsym.-*Triazine* Group  Polymeric Cyanogen Compounds, *Cyanidine* Group
	—	 *Osotetrazones, Phentetrazines*  *Tetrazine* Group

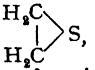
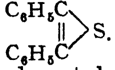
upon a technical scale, because of their colouring and therapeutic properties. This is true of the dyes of the *paroxazine, parathiazine*, and *paradiazine* series—*e.g., resorufin, methylene blue, toluylene red, safranine,* etc.; the dyes of the *thiazole* group, and also of the important febrifuges, like *antipyrine, salipyrine, tolypyrine,* belonging to the pyrazole-group, and *piperazine* or hexa-hydropyrazine, etc.

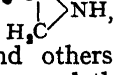
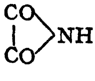
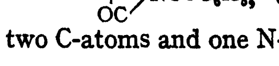
1. THREE-MEMBERED HETEROCYCLIC COMPOUNDS.

As a rule, bodies of this class manifest " ring-strain " to a greater degree than the carbocyclic substances of the trimethylene series. That is, they are inclined, in consequence of a rupture of the ring, to take on additional atoms or atom groups. Hence, they are produced only under the most favourable conditions, and many compounds which formerly were regarded as based upon three-membered heterocyclic rings have, as a result of more recent study and investigation, had their formulæ doubled, or have been discovered to be still higher steps in polymerization (compare *ethyleneimine, glycolide,* etc.).

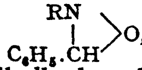
A. MONOHETERO-ATOMIC THREE-MEMBERED RINGS.

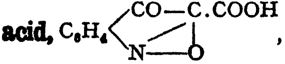
(*a*) Having an O-member: **Ethylene oxide,** . The method of preparing this compound and its properties have already been described in connection with glycol of the aliphatic series. It exhibits a great inclination toward a rupture of the ring. This is shown by the fact that it precipitates the hydroxides from solutions of the metals with the simultaneous formation of glycolacidylhydrins. The same tendency is observed with the substituted ethylene oxides, like *tetramethylethylene oxide,* the *glycide derivatives,* condensed nuclei containing the ring of ethylene oxide—*e.g., tetrahydronaphthylene oxide* and *diketotetrahydronaphthylene oxide* (Vol. II, p. 686), etc.

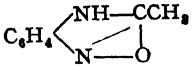
(*b*) Having an S-member: **Ethylene sulphide,** , corresponding to ethylene oxide, is apparently not capable of existing. It is usually its polymerides which are obtained: $(C_2H_4S)\times$ and $(C_2H_4S)_2$ diethylene disulphide; compare *tolane sulphide,* . See also the addition products of sulphur with ethylene and acetylene derivatives (B. **28,** 1635; **30,** 110).

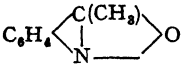
(*c*) Having an N-member: **Ethylene imine,** , also appears unstable. Ethylenediamine hydrochloride and others rather yield the six-membered ring of piperazine. It is assumed that **oxalimide,**  (I. 483), as well as the *lactimides, e.g.,* benzoyl-amino-cinnamic acid lactimide, , contain a three-membered ring consisting of two C-atoms and one N-atom.

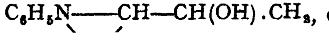
B. DIHETERO-ATOMIC THREE-MEMBERED RINGS.

Rings, consisting of C, N, and O, are assumed to be present in the nitrogen ethers of some of the aldoximes—*e.g.*, the *N*-**alkyl benzaldoximes,** 

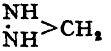
which are resolved by acids into benzaldehyde and *N*-alkylhydroxylamines. The same ring occurs in different polycyclic substances—*e.g.*, the isatogen compounds, such as **isatogenic acid,** 

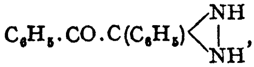
, and in the products obtained by reducing acylated *o*-nitranilines with ammonium sulphide—*e.g.*, 

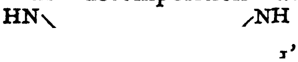
(see benziminazole), etc. Compare also anthranil and anthroxan aldehydes. **Methyl anthranil,** 

phenyl anthranil, anthroxan aldehyde, and **anthroxanic acid**; compare also **furoxan.** Thialdolaniline, 

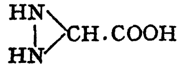
contains a ring consisting of C, N, and S. The same may be observed of similarly formed compounds (see Usèbe's green, Vol. II. 588).

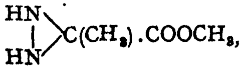
Hydrazi- and Azimethylene-group: Substances consisting of two N- and one C-atom are much better known. The hydrazi-derivatives belong in this class. They are obtained from the hypothetical *hydrazimethylene,*  $\genfrac{}{}{0pt}{}{NH}{NH}>CH_2$ (Curtius, J. pr. Ch. [2], **44,** 169, 554). They are produced in the action of hydrazine upon *o*-diketones and *α*-ketone carboxylic esters (I. 328)—*e.g.*, benzil, diacetyl, pyroracemic ester:

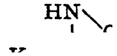
Benzoyl-phenyl-hydrazimethylene, 

, melts with decomposition at 151°, and **diphenyl-dihydrazimethylene,** 

, melts at 147°. *Carboxylic acids* of this result from the reduction of esters of the diazo-fatty acids:

Hydraziacetic acid, 

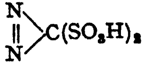
(I. 405), and **hydrazipropionic methyl ester,** 

melting at 82°. The potassium salt of a **sulpho-hydraziacetic ester,** 

has been made by the action of potassium sulphite upon diazoacetic ester (B. **28,** 1848).

The hydrazo-compounds are readily changed by oxidation to the azo-derivatives containing two atoms less of hydrogen.

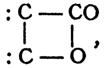
The diazo-compounds of the aliphatic series are obtained from **azimethylene** or **diazomethane.** The latter is produced when nitrosomethylurethane is digested with methyl alcoholic potash. Compare Vol. I. 213 for its properties. It also results from the reduction of methyl nitramine (I. 169; B. **29**, 961), and from the action of hydroxylamine upon methylchloramine (I. 169; B. **28**, 1682).

Diazo-acetic ester (I. 402), **diazopropionic ester** (I. 410), **diazo-succinic ester** (I. 567), and **diazomethane disulphonic acid**,  $\begin{matrix}N\\ \| \\ N\end{matrix}\!\!>C(SO_3H)_2$ (I. 454), are derivatives of diazomethane.

Aromatic derivatives are: **Phenyl-diazo-methane**, **diazo-acetophenone**, **azibenzil**, and **azo-camphor**. Compare also **diazo-indoles**, **diazo-indazoles**, and **diazotetrazoles**.

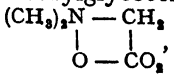
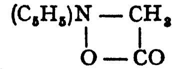
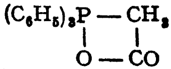
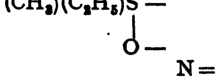
2. FOUR-MEMBERED HETEROCYCLIC SUBSTANCES.

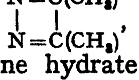
A. MONOHETERO-ATOMIC FOUR-MEMBERED RINGS.

Trimethylene oxide, $CH_2<\genfrac{}{}{0pt}{}{CH_2}{CH_2}>O$ (I. 318), is a homologue of ethylene oxide. Its properties are not well known. The internal anhydrides of certain aromatic β-hydroxycarboxylic acids, *β-lactones* of the common formula  $\begin{matrix}:C-CO\\ | \quad\;\; | \\ :C-O\end{matrix}$, also belong in this class. Compare also dimethyl malic acid lactone, Vol. I.

Trimethylene imine, $CH_2<\genfrac{}{}{0pt}{}{CH_2}{CH_2}>NH$, corresponding to trimethylene oxide, is produced, together with β-methylpyridine, on heating trimethylenediamine hydrochloride.

B. DIHETERO-ATOMIC FOUR-MEMBERED RINGS.

1. The most important bodies containing four-membered rings with two adjacent hetero-atoms are the *cyclic salts*, showing a structure analogous to that of **betaïne**, therefore grouped under the name *betaïnes*. All carboxylic acids form betaïnes if they contain in the α-position a group similar to ammonium hydroxide. Just as trimethylglycocoll hydrochloride, $ClN(CH_3)_3.CH_2.COOH$, yields betaïne,  $\begin{matrix}(CH_3)_3N-CH_2\\ | \qquad\quad | \\ O-CO_2\end{matrix}$, so pyridine-chloracetic acid, $ClN(C_5H_5)CH_2.COOH$, forms **pyridine-betaïne**,  $\begin{matrix}(C_5H_5)N-CH_2\\ | \qquad | \\ O-CO\end{matrix}$ (*q.v.*); triphenylphosphine-chloracetic acid, $ClP(C_6H_5)_3CH_2COOH$, **triphenylphosphorbetaïne**,  $\begin{matrix}(C_6H_5)_3P-CH_2\\ | \qquad | \\ O-CO\end{matrix}$ (B. **27**, 273), and methyl-ethyl sulphide-bromacetic acid, $BrS(CH_3)CH_2.COOH$, yields *methyl ethyl thiobetaïne*, **methyl ethyl thetine**,  $\begin{matrix}(CH_3)(C_2H_5)S-\text{---}\\ | \\ O-\end{matrix}$

Dimethylaziethane,  $\begin{matrix}N=C(CH_3)\\ | \qquad | \\ N=C(CH_3)\end{matrix}$, produced on mixing equimolecular quantities of hydrazine hydrate and diacetyl, and probably also **hydrazulmine** and **azulmic acid**, formed by the interaction of ammonia and cyanogen, contain four-membered rings with two adjacent N-atoms.

2. The cyclic *alkylidene-*, *carbonyl-*, and *thio-carbonyl-ureas*, *-thioureas*, and *-ψ-thioureas*, contain rings with alternating C- and hetero-atoms:

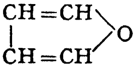
Methylene urea, $CO<{}^{NH}_{NH}>CH_2$, and **methylenethiourea,** are obtained by the action of chlormethyl alcohol upon urea and thiourea (M. **12**, 90); **ethylideneurea** and **-thiourea** are similarly formed from acetaldehyde; **methylene-diphenyl - ψ - thiourea,** $C_6H_5N:C<{}^{S\text{———}}_{N(C_6H_5)}>CH_2$, from diphenylthiourea and CH_2I_2 (Vol. II. p. 102); **carbonyl-thiocarbanilide,** $C_6H_5N:C<{}^{S\text{———}}_{N(C_6H_5)}>CO$, melting at 87°, from diphenylthiourea and $COCl_2$, as well as by desulphurizing **thiocarbonylthiocarbanilide,** $C_6H_5.N:C<{}^{S\text{———}}_{N(C_6H_5)}>CS$, melting at 79°, which results from the interaction of $CSCl_2$ and diphenylurea (B. **25**, 1459).

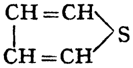
3. FIVE - MEMBERED HETEROCYCLIC SUBSTANCES.

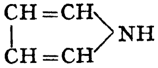
A. MONOHETERO-ATOMIC FIVE-MEMBERED RINGS.

Furan (Furfurane),* Thiophen (Selenophen), Pyrrole.†

The members of the furan, thiophen, and pyrrole group contain five-membered monohetero-atomic rings. They form a closely allied family from the standpoint of methods of formation and chemical behaviour. The parent compounds of these groups contain, in the ordinary sense of the term, a chain of four CH: groups, which is closed as a ring by O :, S : or NH :


Furan.


Thiophen.


Pyrrole.

The parent bodies and their numerous derivatives, especially the thiophens, manifest a great and, in the latter instance, a very remarkable similarity to benzene and its compounds, inasmuch as many of them show the reactions peculiar to benzene derivatives in contradistinction to the fatty substances.

The production of blue-violet and violet-red dyes in the action of isatin and phenanthraquinone with sulphuric acid upon furan, pyrrole, and thiophen compounds is particularly noteworthy.

The *common methods* of forming furan, thiophen, and pyrrole derivatives from γ-diketo-compounds have frequently been mentioned after the description of the latter bodies:

Furans result by the elimination of water from the γ-diketones;

Phosphorus sulphide (P_2S_5) converts γ-diketones into thiophens.

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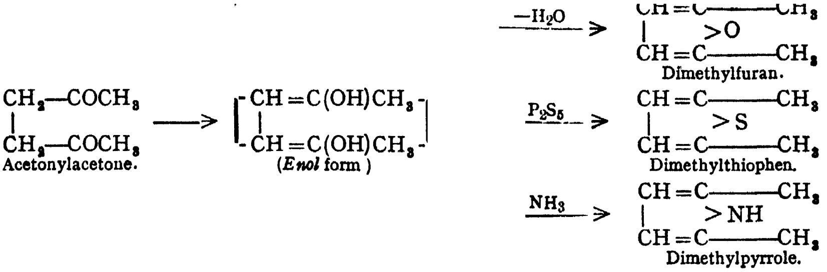
[*] The compound $\begin{array}{l}CH=CH\diagdown\\ |\qquad\qquad\ \ >O\\ \text{———}\ \ \text{———}\diagup\end{array}$ is called *furan*, the name *furfuryl* representing the group $C_4H_3O{\cdot}CH_2$, while C_4H_3O— is called *furyl*.

[†] Compare C. Paal, "Furfuran, Thiophen, und Pyrrolsynthesen," Würzburg, 1890.

Pyrroles are produced by the action of ammonia or primary amines upon γ-diketones:



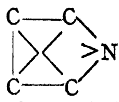
Here the γ-diketones react as unsaturated αδ-glycols. The furans, the thiophens, and pyrroles may be considered as the cyclic anhydrides, sulphides, and imines of the latter. Furans, thiophens, and pyrroles are also obtained by distilling mucic and isosaccharic acids alone or with BaS, and in the distillation of their ammonium salts.

These syntheses harmonize with the accepted structural formulas for furan, pyrrole, and thiophen.

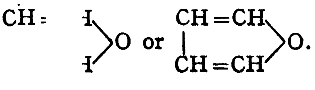
The peculiar aromatic character of these compounds is intelligible if Thiele's views of the benzene nucleus are transferred to the present ring systems, with the assumption that in the three five-membered rings the sulphur, nitrogen, or oxygen atom can to some extent assume the character of a double link by an exercise of its higher

C —C ,

valency (B. **37**, 4254; C. 1905, II. 1797). On formulæ like

and  NH, see B. **24**, 1347, 1758. On desmotropic formulæ of pyrrole see below.

To distinguish the possible isomerides, the replaceable hydrogen atoms of the methine groups in furan, thiophen, and pyrrole are designated by numbers or letters, as with benzene:



The positions 2 and 5 are equal in value; also 3 and 4. The first are also termed α-, the latter β-positions. It is obvious that the monoderivatives of furan, thiophen, and pyrrole can exist in two isomeric forms (α-derivatives and β-derivatives).

The C-disubstitution products occur in four forms, as αα-, αβ-, αβ¹-, and ββ-, derivatives.

1. THE FURAN GROUP.

Furan (Furfurane), C_4H_4O, boiling at 32°, was first obtained by distilling barium pyromucate (p. 18) (Limpricht, 1870; C. 1897, II. 268): ($C_4H_3O.CO_2H = C_4H_4O + CO_2$). It is present in the distillation products of pine wood. It is a liquid insoluble in water, and has a peculiar odour.

By conducting its vapours with hydrogen over finely divided nickel heated to 170°, it is reduced to tetrahydrofuran or tetramethylene oxide (C. 1908, I. 1630). With isatin and phenanthrene quinone it forms dyes. It reacts very violently with hydrochloric acid, and forms a brown amorphous substance (like pyrrole red, p. 28). A pine shaving moistened with hydrochloric acid assumes a green colour when brought in contact with the vapours of furan.

By means of methyl alcoholic HCl, furan can be split up to form the tetramethylacetal of succindialdehyde (Ch. Ztg., 1900, 857).

Bromo-furan can be obtained from brom-pyromucic acids, or by the direct action of bromine upon furan. Addition products result from an excess of bromine.

Di-iodo-furan, m.p. 47°, from the K salt of dehydromucic acid with iodine at 100° (Am. Ch. J., **25,** 439).

β(?)-**Nitro-furan,** m.p. 28°, volatile with steam, is formed by nitrating furan with fuming HNO_3 in acetic anhydride. An aldehyde (nitro-succin-aldehyde ?) seems to be formed as an intermediate product (C. 1902, I. 1106). A **dinitro-furan,** m.p. 101°, is formed by nitrifying nitrofuran or nitropyromucic acid.

α-**Amino-furan** has been obtained in the form of its urethanes from pyromucic azide by boiling with alcohols; also β-**amino-furan** in the form of its acetyl derivative, m.p. 112°, from acetamino-pyromucic acid by splitting off CO_2. The free amines could not be obtained from these derivatives, since on saponification they split off NH_3 (J. pr. Ch. [2], **65,** 38; C. 1903, II. 292).

Methylfuran, $C_4H_3(CH_3)O$, is in all probability *sylvane,* which occurs in pine-tar oil. It boils at 63° (B. **18,** 879).

It can also be obtained from creosote from beechwood tar. On splitting up with HCl it yields lævulinaldehyde, $CH_3COCH_2CH_2CHO$ (B. **31,** 37).

α,α_1-**Dimethylfuran,** $C_4H_2(CH_3)_2O$, is formed by the distillation of carbopyrotritartaric acid, and has been synthesized from acetonyl acetone upon heating it with $ZnCl_2$ or P_2O_5. It boils at 94°.

It regenerates acetonylacetone when it is heated with dilute hydrochloric acid to 170°.

α,α_1-**Phenyl-methylfuran,** $C_6H_5.C_4H_2(CH_3)O$, is produced from acetophenoneacetone (B. **17,** 915 and 2759). It melts at 42° and boils at 235°–240° C. Sodium and alcohol convert it into a **tetrahydro-**compound.

Diphenylfuran, melting at 91°, is obtained from diphenacyl (B. **23,** R. 743; **26,** 1447). **Triphenylfuran,** melting at 93°, is formed from desylacetophenone (B. **21,** 2933; **26,** 61). **Tetraphenylfuran,** *Lepidene* (B. **22,** 2880), melting at 175°, is produced, together with benzil, when benzoïn is heated with hydrochloric acid to 130°.

The acetate of a β-**hydroxy-triphenylfuran,** m.p. 135°, is obtained from dibenzoyl styrene with acetic-sulphuric acid (B. **31,** 1248). The so-called **carlina oxide,** obtained from the ethereal oil of *Carlina acaulis,* m.p. 167°, is perhaps 1-phenyl-3,α-furylallene (B. **42,** 2355).

Furfuro-stilbene, $C_4H_3O—CH=CH—C_4H_3O$, melting at 101°, is the stilbene of the furan series. It results upon heating polymeric thiofurfural (B. **24,** 3591).

Furfuryl alcohol, $C_4H_3O.CH_2OH$, is a colourless syrup, which is coloured green by hydrochloric acid. It results from the action of sodium amalgam and acetic acid upon the aldehyde furfurol, but more easily by treatment with aqueous caustic potash (B. **19,** 2154). Furfurane carboxylic acid is produced at the same time ($2C_4H_3O.CHO + H_2O = C_4H_3O.CH_2OH + C_4H_3O.CO_2H$) (B. **19,** 2154).

Furfur alcohol is found in considerable quantities in the coffee oil of roasted coffee; **diphenyl carbaminic ester,** $C_4H_3O[CH_2OCON(C_6H_5)_2]$, m.p. 98° (B. **35,** 1846, 1855).

Furfuryl methyl ether, $(C_4H_3O).CH_2.O.CH_3$, boils at 134°–136° (B. **26,** R. 239).

Furfurylamine, $C_4H_3O.CH_2.NH_2$, boiling at 146°, results in the reduction of furfuronitrile and furfurol hydrazone (see below).

***n*-Propyl-α-furfuryl carbinol** $(C_4H_3O)CH(OH).C_3H_7$, b.p.$_{12}$ 93°, form furfurol and propyl magnesium bromide (C. 1910, I. 450); several tertiary α-furfuryl carbinols and αα′-furfuryl dicarbinols have been obtained by the action of alkyl magnesium haloids upon pyromucic esters and dehydro-mucic ester (C. 1906, I. 851).

Furfural* (**Furfuraldehyde**), $C_5H_4O_2 = C_4H_3O.CHO$, boiling at 162°, with the sp. gr. 1.163, is the aldehyde of pyromucic acid, and is produced in the distillation of bran (*furfur,* Fownes, 1849), or of sugar (Dōbereiner, 1831), and wood, as well as most carbohydrates and glucosides, with dilute sulphuric acid. When present in even the merest traces it can be detected by the red coloration given by aniline or xylidine (B. **20,** 541).

Furfural is produced quantitatively when pentoses like arabinose, etc., are distilled with hydrochloric acid. Various analytical methods for the estimation of the pentoses are based on this fact (B. **28,** R. 629). Glycuronic acid, when heated with hydrochloric acid, breaks down into furfural, water, and CO_2 (B. **29,** R. 280).

Furfural is a colourless liquid with an aromatic odour. It is fairly soluble in water and very soluble in alcohol. It becomes brown on exposure to the air, and shows all the properties of an aldehyde. It combines with bisulphites, passes into furfuryl alcohol under the influence of sodium amalgam, and is changed to pyromucic acid by silver oxide, and to the alcohol and acid through the action of caustic potash.

By the oxidation of furfurol with hydrogen peroxide or Caro's acid we obtain **oxyfurfurals,** $C_4H_2O(OH)(CHO)$, which give characteristic colour reactions with phenols (B. **33,** 3132). It yields **furfuraldoxime** with hydroxylamine; this melts at 89° and boils at 205°. It unites similarly with phenylhydrazine, forming a *hydrazone*, melting at 96°. With orthoformic ester it yields the *acetal*, $C_4H_3O.CH(OC_2H_5)_2$, boiling at 187° to 190° (B. **29**, 1008).

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* This is often called furfurol, but this name is better avoided, as it implies the presence of a hydroxy group.

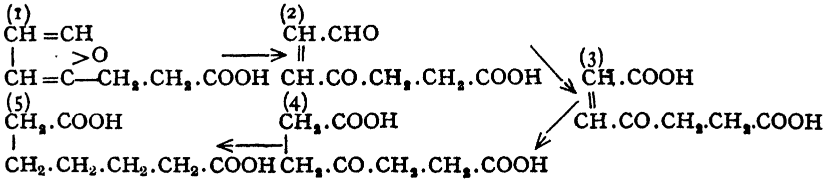
Furthermore, furfural manifests *all the condensation reactions of benzaldehyde* (see below). (1) It combines with dimethylaniline to form a green dye-stuff, corresponding to malachite green. (2) It condenses with aldehydes and ketones of the fatty series to furfurane aldehydes and ketones with unsaturated side-chains. This reaction occurs quite readily on digesting with dilute caustic soda (B. **13**, 2342). Thus, with acetaldehyde it forms **furfur-acroleïn**, $C_4H_3O.CH : CH.CHO$, melting at 51°; with acetone, **furfur-acetone**, $C_4H_3O.CH:CH.CO.CH_3$; with acetophenone, **furfural-mono-** and **diacetophenone**, and **difurfural triacetophenone** (B. **29**, 2248). (3) Just as potassium cyanide in alcoholic solution changes benzaldehyde to benzoin, so it converts furfurol into **furoin**, $C_{10}H_8O_4$, melting at 135°; $2C_4H_3O.CHO = C_4H_3O.CH(OH).CO.C_4H_3O$. This is in every way similar to benzoïn. Furoïn is oxidized in alkaline solution by the oxygen of the air to **furil**, $C_4H_3O.CO.CO.C_4H_3O$. This corresponds to benzil. Tin and hydrochloric acid reduce it to desoxyfuroïn, $(C_4H_3O)CH_2.CO(C_4H_3O)$ (B. **28**, R. 992). Furil digested with caustic potash becomes **furilic acid**, $(C_4H_3O)_2C(OH)COOH$, analogous to benzilic acid. Compare B. **25**, 2843, for the condensation products of furoïn with *o*-diamines.

Furfurane **acids**, with unsaturated side-chains, are produced, in the condensation of furfural and fatty acids, on heating it with the anhydrides and sodium salts of the fatty acids. This is analogous to the formation of cinnamic acid from benzaldehyde. Furyl-acrylic acid results on heating furfurane with acetic anhydride and sodium acetate:

$$C_4H_3O.CHO + CH_3.CO_2Na = C_4H_3O.CH : CH.CO_2Na + H_2O.$$

Furyl-acrylic Acid, $C_7H_6O_3$, melting at 141°, is also formed from *furfur-malonic acid*, the condensation product of furfurol and malonic ester (B. **24**, 143; **27**, 283). Furyl-acrylic acid, like cinnamic acid, occurs in a *stereoisomeric modification* (B. **28**, 129). The acid, when heated with hydrochloric acid, has its ring decomposed, and acetone diacetic acid results. Sodium amalgam converts it into

Furyl-propionic Acid (1), $C_4H_3O.CH_2.CH_2.CO_2H$, melting at 51°. Bromine-water disrupts the furfurane ring in this compound, and the product is *furon-aldehyde* (2), which can be gradually converted step by step into furonic acid (3), hydrofuronic acid, or, γ-ketopimelic acid (4) and pimelic acid (5):



This conversion of furfural into *n*-pimelic acid proves that the aldehyde group is in the *a*-position.

Furyl-angelic Acid, $C_4H_3O.CH:C(CH_2.CH_3).COOH$, from furfural and butyric acid, melts at 88°, and passes into the corresponding **Furyl-valeric Acid** under the influence of sodium amalgam.

Furfural condenses with lævulinic acid, depending upon whether alkaline or acid solvents are employed, either to δ- or β-**Furfur-lævulinic Acid,** $C_4H_3O.CH:CH.CO.CH_2.CH_2.COOH$, or $C_4H_3O.CH:$-$C(CO.CH_3).CH_2COOH$. The latter changes readily with *benzene ring formation* into hydroxyacetocoumarone (p. 40).

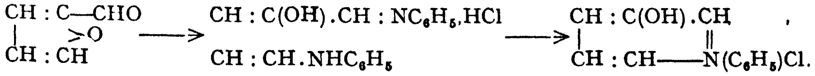
From furfural and succinic acid the following have been obtained under different conditions:

Furfursuccinic acid, $(C_4H_3O)CH:C(CO_2H).CH_2CO_2H$; **difurfursuccinic acid,** $(C_4H_3O)CH:C(CO_2H).C(CO_2H):CH(C_4H_3O)$; and **difurfur propionic acid,** $(C_4H_3O)CH:CH.C(CO_2H):CH(C_4H_3O)$ (B. **34**, 1626; C. 1904, I. 925).

Hydrofurfuramide, $(C_5H_4O)_3N_2$, melting at 117°, results from the action of aqueous ammonia upon furfural (as hydrobenzamide from benzaldehyde; *q.v.*).

Boiling water decomposes it into furfural and ammonia. If boiled with KOH it undergoes a transposition into the isomeric base, **Furfurin,** melting at 116° (compare glyoxalines).

By the action of primary aromatic amines and their salts upon furfural, the furfurane ring is broken up, and strongly coloured arylamine derivatives of β-oxyglutaconic aldehyde are formed. Their hydrochlorides, on boiling with alcohol, split off 1 mol. arylamine and pass into N-aryl-β-oxy-pyridinium salts (B. **38**, 4112):



α-**Methyl furfural,** $C_4H_2(CH_3)O.CHO$, boiling at 184°–186°, occurs together with furfural in wood oil (B. **22**, 608). It is also present in the product obtained by distilling varec with sulphuric acid. When rhamnose (I. 619) is distilled with sulphuric acid, it results, just as furfural is obtained from arabinose (B. **22**, R. 752).

ω-**Oxy**-α-**methylfurfural,** $(C_4H_2O)(CH_2OH)CHO$, b.p.$_0$ 70°, is formed in the dry distillation of cellulose, and on heating hexoses with aqueous oxalic acid under pressure. The corresponding halogen hydride esters, **chloro-** and **bromo-methylfurfural,** m.p. 60°, are obtained by the action of HCl and HBr upon ketoses or cellulose (B. **43**, 2795).

Ketones of the Furfurane Series.—α-**Acetyl-furan,** $C_4H_3O(COCH_3)$, m.p. 33°, b.p.$_{10}$ 67°, is found in wood-tar, and is obtained synthetically by the splitting up of furoyl acetic ester, $C_4H_3O.CO.CH_2$-$CO_2C_2H_5$, b.p.$_{10}$ 143°, the condensation product of pyromucic ester and acetic ester (C. 1898, I. 327; B. **33**, 492; C. 1911, I. 81). α-**Furyl-acetone,** $(C_4H_3O)CH_2COCH_3$, bp. 180° (C. 1906, I. 669). α-**Benzoyl-furan,** $C_4H_3O(COC_6H_5)$, b.p.$_{19}$ 164°, is obtained from pyromucic chloride, benzene, and $AlCl_3$ (C. 1900, I. 299). $\alpha\alpha_1$-**Dibenzoyl furan,** m.p. 107°, from dehydro-mucic chloride with benzene and $AlCl_3$. $\alpha\alpha_1$-**Phenyl-methyl**-β-**acetyl-furan,** m.p. 57°, from phenacyl-diacetyl-methane (C. 1902, I. 1164).

Carboxylic Acids of Furfurane.—**Furan-α-carboxylic Acid** (compare C. 1897, II. 268), $C_4H_3O.CO_2H$, *pyromucic acid*, melting at 134° with sublimation, is obtained by the oxidation of furfural, and in the distillation of mucic and *iso*saccharic acids (Vol. I.); it therefore contains the carboxyl group in the α-position.

History.—Scheele, in 1780, observed pyromucic acid as a product of the distillation of mucic acid. Pelouze (1834) determined its composition, and v. Baeyer established its constitutional formula.

Its *ethyl ester*, $C_4H_3O.CO_2.C_2H_5$, melts at 34° and boils at 210° C. Its *chloride*, $C_4H_3O.COCl$, boils at 170°. Ammonia converts this into an *amide*, $C_4H_3O.CO.NH_2$, which is changed into *pyromuconitrile*, $C_4H_3O.CN$, by PCl_3. The nitrile can also be obtained from furfuraldoxime by the exit of water. See C. 1897, I. 1024, for the *hydrazide*, *azide*, etc.

Bromine vapour converts pyromucic acid into a *tetrabromide*, $C_4H_3OBr_4.CO_2H$, which is oxidized to dibromsuccinic acid by chromic acid. Fumaric acid results on evaporating pyromucic acid with bromine water. An excess of bromine or chlorine water produces mucobromic acid and mucochloric acid (I, 402).

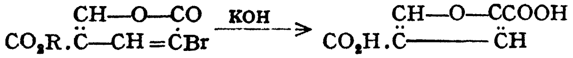
α-Brom-pyromucic Acid, $C_4H_2BrO.CO_2H$, is formed by heating the tetrabromide, and by brominating pyromucic acid in glacial acetic acid solution. It melts at 184° (B. **19**, R. 241). **β-Brompyromucic Acid,** from the two dibrompyromucic acids and zinc, melts at 129° (B. **17**, 1759).

Nitropyromucic Acid, $C_4H_2(NO_2)O.CO_2H$, melting at 183°, is formed by nitrating furan-dicarboxylic acid and by oxidizing ω-nitrovinylnitrofuran (B. **18**, 1362).

Its ethyl ester, on reduction with Al amalgam, gives **amino-pyromucic ester,** $C_4H_2O(NH_2)CO_2C_2H_5$. Its acetyl derivative is saponified by potash to *acetamino-pyromucic acid* (C. 1902, II. 1097; 1903, II. 292).

α,α₁-Furan dicarboxylic Acid, $C_4H_2O(CO_2H)_2$, *dehydromucic acid*, is produced by heating mucic acid to 100° with hydrochloric acid. It dissolves with difficulty in water, and when heated breaks down into carbon dioxide and pyromucic acid. The esters are all solid, and show interesting melting-point regularities: **Dimethyl ester,** m.p. 112°, b.p.$_{15}$ 155°; **diethyl ester,** m.p. 47°; **chloride,** m.p. 80°.

αβ₁-Furan dicarboxylic acid, m.p. 266°, **dimethyl ester,** m.p. 110°, is formed from bromo-cumalinic ester with potash (B. **34**, 1992):



$$\begin{array}{c}\text{CH—O—CO}\\ \text{CO}_2\text{R}.\ddot{\text{C}}\text{—CH}=\dot{\text{C}}\text{Br}\end{array} \xrightarrow{\text{KOH}} \begin{array}{c}\text{CH—O—CCOOH}\\ \text{CO}_2\text{H}.\ddot{\text{C}}\text{———}\ddot{\text{C}}\text{H}\end{array}$$

Homologous furan-carboxylic acids can be obtained synthetically from γ-diketone carboxylic esters by the removal of water.

Methylpyromucic Acid, $C_4H_2(CH_3)O.COOH$, melting at 109°, obtained from methyl furfural by oxidation; its chloride, m.p. 28°, b.p. 202°, gives on bromination a dibromo-substitution product, which on treatment with water gives **aldehydo-pyromucic acid,** $C_4H_2O(COOH)(CHO) + H_2O$, m.p. 202°, which oxidizes to dehydromucic acid (C. 1898, I. 933).

α,α_1-**Dimethylfuran-β-carboxylic Acid, Pyrotritaric Acid,** $C_4H(CH_3)_2O.CO_2H$ (B. **20,** 1074), **Uvinic Acid,** melting at 135° C., may be obtained (1) from acetonylacetoacetic ester; (2) from carbopyrotritaric acid and from methronic acid by the splitting-off of carbon dioxide; (3) from tartaric acid by distillation; (4) from pyroracemic acid by protracted boiling with baryta-water or sodium acetate, etc.

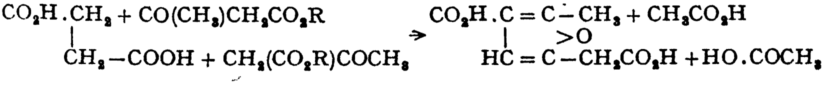
When heated to 150°–160° with steam it breaks up into carbon dioxide and acetonylacetone. Rapidly distilled, it decomposes into carbon dioxide and dimethylfuran.

α,β_1-**Dimethylfuran-β-carboxylic Acid,** melting at 122°, is isomeric with pyrotritaric acid. It is formed (1) from brom*iso*dehydracetic acid instead of the expected $\alpha\beta_1$-dimethyl-$\beta\alpha_1$-furfurane dicarboxylic acid; (2) by the condensation of acetoacetic ester with chloracetone; (3) from **β-methyl-furan-α-acetic-β-carboxylic acid,** m.p. 196°, by elimination of CO_2 (B. **35,** 1545).

α,α_1-**Methylphenylfuran-β-carboxylic Acid,** $C_4H(CH_3)(C_6H_5)O.CO_2H$, from acetophenone-acetoacetic ester, melts at 181°, and when heated breaks down into CO_2 and methylphenylfuran (B. **17,** 2764).

α,α_1-**Dimethylfuran-β,β_1-dicarboxylic Acid,** $C_4(CH_3)_2O(CO_2H)_2$, **carbopyrotritaric acid,** melting at 261°, results upon boiling diacetsuccinic ester with dilute sulphuric acid (Knorr, B. **17,** 2864; **22,** 146). Carbopyrotritartaric acid at higher temperatures breaks up into carbon dioxide and pyrotritartaric acid.

Methronic acid, α-**methylfuran-α_1-aceto-β-carboxylic acid,** $C_8H_8O_5$, m.p. 204°, is isomeric with carbopyrotritaric acid, and also yields on splitting off CO_2 pyrotritaric acid. It is formed (1) from acetoacetic ester and Na succinate in the presence of acetic anhydride (B. **18,** 3410), which may be formulated as follows (B. **39,** 2129):

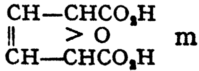
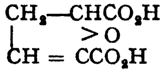


$$\begin{array}{l} CO_2H.CH_2 + CO(CH_3)CH_2CO_2R \\ \quad | \\ \quad CH_2-COOH + CH_2(CO_2R)COCH_3 \end{array} \rightarrow \begin{array}{l} CO_2H.C = C-CH_3 + CH_3CO_2H \\ \qquad | \qquad\quad >O \\ \qquad HC = C-CH_2CO_2H + HO.COCH_3 \end{array}$$

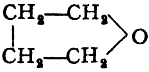
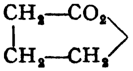
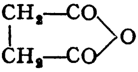
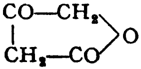
Similarly, acetoacetic ester and pyrotartaric acid gives methyl methronic acid.

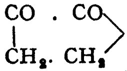
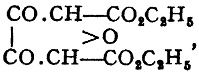
(2) By condensation of acetoacetic ester with glyoxal, together with sylvane-acetic ester containing less CO_2 (B. **21,** R. 636; **22,** 152; A. **250,** 166).

Hydrofurans.—But few hydrofuran derivatives have been obtained by the reduction of furans—*e.g., tetrahydro*-α,α_1-*methylphenylfuran,* $C_4H_6(CH_3)(C_6H_5)O$, boiling at 230°, from methylphenylfuran, *tetrahydrodiphenylfuran* (B. **23,** R. 744), etc.

By reduction of dehydromucic acid with sodium amalgam at 0° in a current of CO_2 we get the so-called (α) (cis)-**Dihydro-α,α_1-furandicarboxylic acid,**  $\begin{array}{l} CH-CHCO_2H \\ \| \qquad > O \\ CH-CHCO_2H \end{array}$ m.p. 150°, which is transposed in alkaline solution to the (β) (trans-) form, m.p. 179°. The latter can be resolved by cinchonine into its optically active components, m.p. 144°. With bromine, both acids combine to form dibromides, which, on treatment with baryta-water, yield pyromucic acid. On prolonged boiling with alkali, the (α) and (β) acids yield (γ) **Dihydrofuran-dicarboxylic acid,**  $\begin{array}{l} CH_2\text{—}CHCO_2H \\ |\qquad\quad >O \\ CH = CCO_2H \end{array}$ (?); in contrast with the (α) and (β) acid, this acid is further reduced by sodium amalgam to **tetrahydrofuran-α,α₁-dicarboxylic acid,** $C_4H_6O(CO_2H)_2$, (α) form, m.p. 95°, (β) form, m.p. 124° (C. 1901, II. 271; 1905, I. 1558).

Synthetically, by reduction of erythritol we obtain **dihydrofuran,** C_4H_6O, b.p. 67°, which is transformed by PCl_5 into furan (Bull. soc. chim., **35,** 418). α-**Methyl-dihydrofuran,** $C_4H_5(CH_3)O$, is formed from aceto-propyl alcohol (see Vol. I. and B. **22,** 1196). $\alpha\alpha_1$-**Diphenyl-dihydrofuran,** $C_4H_4(C_6H_5)_2O$, m.p. 89°, is obtained from α-phenyl-cinnamyl-acrylic acid dibromide with alkalies (A. **306,** 210). Further **dihydrofuran derivatives** have been obtained synthetically from α-chloro-crotonic ester and chloro-fumaric ester by condensation with sodium acetoacetic ester and sodium benzoyl-acetic ester (B. **29,** R. 859).

Tetramethylene oxide,  $\begin{array}{l} CH_2\text{—}CH_2 \\ |\qquad\quad >O \\ CH_2\text{—}CH_2 \end{array}$, and its homologues (I. 299) are tetrahydrofurans; the γ-lactones—*e.g.*, **butyrolactone,**  $\begin{array}{l} CH_2\text{—}CO_2 \\ |\qquad\quad >O \\ CH_2\text{—}CH_2 \end{array}$ (I. 345)—and the anhydrides of the succinic acid series—*e.g.*  $\begin{array}{l} CH_2\text{—}CO \\ |\qquad\quad >O \\ CH_2\text{—}CO \end{array}$ (I. 447), etc.—are keto- and diketotetrahydrofurans. **Tetronic acid,**  $\begin{array}{l} CO\text{—}CH_2 \\ |\qquad\quad >O \\ CH_2\text{—}CO \end{array}$ (I. 544), and its homologues are isomeric with the latter.

Also the α-ketolactones of the formula  $\begin{array}{l} CO\ .\ CO \\ |\qquad\quad >O \\ CH_2 .\ CH_2 \end{array}$, which are obtained by the condensation of α-ketonic acids with aldehydes (B. **31,** 2218). **β,β′-Diketo-tetrahydrofuran-αα′-dicarboxylic acid diethyl ester,**  $\begin{array}{l} CO.CH\text{—}CO_2C_2H_5 \\ |\qquad\quad >O \\ CO.CH\text{—}CO_2C_2H_5 \end{array}$, m.p. 189°, is formed by the oxidation of oxalic ester and ethyl glycollic ester by means of sodium ethylate (C. 1906, II. 1433).

2. THIOPHEN GROUP.*

Thiophen, C_4H_4S, an analogue in constitution of furan, C_4H_4O, exhibits the greatest similarity to benzene. It may be viewed as benzene, in which one of the three acetylene groups, CH : CH, has been replaced by S. By the replacement of the 4-H-atoms in thiophen by other elements or groups we obtain innumerable derivatives, in all respects analogous to those derived from benzene. All thiophen compounds give an intense blue coloration—the indophenin reaction (B. **16,** 1473)—when mixed with a little isatin and concentrated sulphuric acid.

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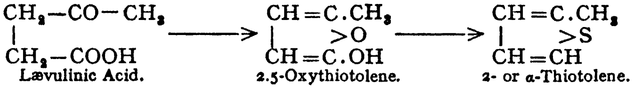
* V. Meyer, "Die Thiophengruppe," 1888.

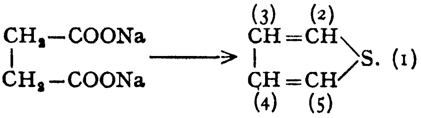
History.—Thiophen, as well as the methylated thiophens, are invariably associated with the benzene hydrocarbons which are prepared technically from coal-tar. Therefore, before thiophen was discovered, the indophenin reaction was considered as characteristic of benzene hydrocarbons. V. Meyer (1883) observed an absence of this reaction when working with a benzene preparation made from benzoic acid, and that it reappeared when commercial benzene containing sulphur was employed in the test. This led to the discovery of thiophen. The same investigator ascertained the constitution of the latter and its kinship to furan and pyrrole. Thionessal, discovered by Laurent in 1841, is a thiophen derivative, but it was only in 1891 that Baumann and Fromm proved it to be tetraphenylthiophen.

The *synthetic methods* of producing thiophen compounds from γ-dicarbonyl derivatives have been discussed (I. 348; III. 13). The more special procedures are the ready conversion of γ-ketone acids into hydroxythiophens by means of P_2S_5, and thiophens result when the primary hydroxythiophens are reduced with P_2S_3 (B. **19**, 551; **28**, 1495):



Lævulinic Acid. 2.5-Oxythiotolene. 2- or α-Thiotolene.

Thiophen, C_4H_4S, boiling at 84°, with sp. gr. 1·062 (23°), occurs in coal-tar (B. **28**, 492), just as do the methylthiophens; indeed, the individual thiophens are present (to upward of 0·6 per cent.) in the corresponding commercial benzene hydrocarbons, as they have the same boiling-points. Thiophen is found in benzene, methylthiophens in toluene, etc. Thiophen is also formed in considerable quantity by heating a mixture of sodium succinate and phosphorus trisulphide (Volhard and Erdmann, B. **18**, 454):



Thiophen also results upon heating crotonic acid, butyric acid, paraldehyde, etc., with phosphorus trisulphide; by conducting ethyl sulphide through tubes heated to redness or passing illuminating gas over heated pyrites, FeS_2, and acetylene or ethylene over boiling sulphur.

Unsaturated aromatic hydrocarbons, when heated with sulphur, yield phenyl thiophens. Thus, styrene forms diphenylthiophen; stilbene, tetraphenylthiophen; also acetylenedicarboxylic acid, thiophen tetracarboxylic acid (B. **28**, 1635; **30**, 110). Thiophen is obtained from crude benzene by shaking it with a little concentrated sulphuric acid (B. **17**, 792).

It can also be extracted by boiling with Hg acetate, in which case the thiophen separates out as thiophen-mercuro-oxy-acetate, which can be fairly easily split up into thiophen and mercuric chloride by boiling with HCl (B. **32**, 758; **38**, 2208).

Thiophen is a colourless liquid with an odour resembling that of benzene. It becomes crystalline when exposed to a mixture of solid carbon dioxide and ether. Sodium has no effect upon it, even when it is heated. Mixed with a little sulphuric acid and isatin, it becomes dark blue in colour. The same occurs when its solution in sulphuric acid is added to phenanthraquinone in glacial acetic acid (reaction of Laubenheimer, B. **19**, 673; **37**, 3348).

It is remarkable that thiophen, which from its formula can be regarded as a cyclic, unsaturated alkylene sulphide, does not exhibit the additive power of normal alkyl sulphides for methyl iodide, oxygen, etc. When thiophen is heated to 200° with piperidine, sulphur is eliminated and a base produced which yields *tetramethylenedipiperidine*, $C_5H_{10}N(CH_2)_4NC_5H_{10}$, upon reduction (B. **28**, 2217).

This very striking analogy existing between bodies of the *thiophen* series and the *benzene* series may be observed with the following representatives of both groups, the boiling and melting points of which compounds are presented in the table. The benzene derivatives have already been discussed; those of thiophen will receive attention in the succeeding pages.

Benzene Series.	B.P.	Thiophen Series.	B.P.
Benzene	80·5°	Thiophen	84°
Toluene	110·3°	Thiotolen	113°
p-Xylene	138°	2 : 5-Thioxen	135°
*iso*Propylbenzene	153°	*iso*Propylthiophen	154°
Diphenyl	254°	Dithienyl	266°
Diphenylmethane	261°	Dithienylmethane	267°
Chlorbenzene	132°	α-Chlorthiophen	130°
p-Dichlorbenzene	172°	Dichlorthiophen	170°
Brombenzene	155°	α-Bromthiophen	150°
Tetrabrombenzene	329°	Tetrabromthiophen	326°
p-Dinitrobenzene	299°	Dinitrothiophen	290°
Benzoic Acid	250°	α-Thiophencarboxylic Acid	260°
Benzonitrile	191°	Thiophen-nitrile	190°
Acetophenone	202°	Acetothienone	213°
Benzophenone	307°	Thienone	326°
Cinnamic Acid .. m.p.	133°	Thienylacrylic Acid .. m.p.	138°

1. *Thiophen Homologues.*—Homologous thiophens, in addition to their synthetic formation from γ-dicarbonyl compounds, are prepared from thiophen according to methods perfectly similar to those used in the production of the corresponding benzene hydrocarbons from benzene; thus, from iodthiophen and an alkyl iodide by means of sodium; from thiophen, alkyl bromides and aluminium chloride, etc. The behaviour of the thiophen homologues, when subjected to oxidation, etc., is analogous to that of the corresponding benzenes.

Methylthiophens.

α-**Thiotolen,** from iodthiophen by the aid of methyl iodide and sodium, is converted into α-thiophencarboxylic acid by oxidation.

β-**Methylthiophen,** β-**Thiotolen,** is formed when sodium pyrotartrate is heated with P_2S_3. Both thiotolens occur in coal-tar.

Dimethylthiophens or **thioxens** occur in crude xylene (B. **29,** 2560). 2,3-**Dimethylthiophen** boils at 136°. 2,4-**Dimethylthiophen** boils at 138°. 2,5-**Thioxen** boils at 135°. 3,4-**Dimethylthiophen** boils at 145°. *iso***Propylthiophen,** boiling at 154°, is formed when aluminium chloride acts upon thiophene and *iso*propyl bromide.

α-**Phenylthiophen,** melting at 41°, is prepared by heating benzoyl propionic acid with phosphorus sulphide (B. **19,** 3140).

α,α_1-**Diphenylthiophen,** melting at 153°, results from diphenacyl and P_2S_5 or from styrene or cinnamic acid with sulphur (B. **28,** 890), together with α,β_1-**diphenyl-thiophen,** melting at 119°. **Tetraphenylthiophen,** *Thionessal,* $C_4(C_6H_5)_4S$, melting at 184°, is produced when thiobenzaldehyde is heated; also from stilbene and sulphur (A. **38,** 320; B. **24,** 3310), just as thiophene is formed from ethylene and sulphur (see above).

Dithienyl, $C_4H_3S.C_4H_3S$, melting at 83° and boiling at 266°, is obtained, like diphenyl, by conducting the vapours of thiophen through tubes heated to redness. An isomeric α,α_1-**Dithienyl,** melting at 33°, results in the action of sulphuric acid upon thiophen, and also by the interaction of α-iodthiophen and silver (B. **27,** 2919; **27,** 2385). **Dithienylmethane,** $(C_4H_3S)_2CH_2$, melting at 43° and boiling at 267°, is formed from thiophen and methylal. **Thienyldiphenylmethane,** $(C_3H_3S).CH(C_6H_5)_2$, melting at 63° and boiling at 335°, is prepared from thiophen and benzhydrol. **Thienyltriphenylmethane,** $(C_6H_5)_3$-$C(C_4H_3S)$, melting at 237°, is formed when P_2O_5 acts upon triphenylcarbinol and thiophen. The homologous thiophens may also be as readily condensed with triphenyl carbinol (B. **29,** 1402).

Dithienylphenylmethane, $C_6H_5.CH(C_4H_3S)_2$, melting at 75°, has been prepared by the condensation of benzaldehyde and thiophen (B. **29,** 2205).

as-**Dithienylethane,** $CH_2CH(C_4H_3S)_3$, b.p. 270° to 280°. *sym.*-**Dithienylethylene,** m.p. 125° (see B. **30,** 2041).

2. *Halogen Derivatives.*—Chlorine and bromine attack thiophen in the cold. The action is even more energetic than with the benzenes. Iodine, in the presence of mercuric oxide, also attacks it at the ordinary temperature. The three halogens first enter the α-position. In properties the haloid thiophens are very similar to the benzene haloids. When the brominated thiophenes are oxidized with strongly cooled, concentrated nitric acid, the ring is ruptured, and there result dibromomaleïc acid, brom-citraconic acid, dibromacetoacrylic acid, etc. (B. **24,** 74, 1347).

α-Alkylthiophens yield on chlorination and bromination, even in sunlight and at boiling-point, almost exclusively nuclear substitution products; but in β-methylthiophen, especially on heating, substitution takes place mostly in the side-chain (C. 1905, II. 1796).

α-**Chlorthiophen,** C_4H_3ClS, boils at 130°, and **dichlorthiophen,** $C_4H_2Cl_2S$, at 170°. **Tetrachlorthiophen,** C_4Cl_4S, melts at 36°, and boils from 220°–240°.

α-**Bromthiophen** boils at 150°. α,α_1-**Dibromthiophen** boils at 211°. Its formation serves for the complete isolation of all the thiophen that may be present in a thiophen-benzene (B. **18,** 1490). **Tribromthiophen** melts at 29° and boils at 260°. **Tetrabromthiophen,** C_4Br_4S, melts at 112° and boils at 326°. It is also produced in the energetic bromination of substituted thiophens when the substitutes are displaced (B. **26**, 2457).

α-**Iodthiophen,** C_4H_3IS, boils at 182°.

3. *Nitro-derivatives.*—The action of nitric acid upon thiophen is so very energetic that, in order to moderate the reaction, air charged with thiophen vapour is conducted into the fuming nitric acid. Mono- and dinitrothiophen are then produced (B. **17**, 2648).

Nitrothiophen, $C_4H_3(NO_2)S$, melts at 44° and boils at 225°.

Dinitrothiophen, $C_4H_2(NO_2)_2S$, melts at 52° and boils at 290°. Caustic potash colours its alcoholic solution dark red. The same coloration of dinitrobenzene, caused in the same way, is due to admixed dinitrothiophen (B. **17**, 2778).

4. *Amino-derivatives.*—Nitrothiophen is reduced with much more difficulty than the nitrobenzenes. The reduction succeeds when zinc and hydrochloric acid are allowed to act upon the dilute alcoholic solution (B. **18**, 1490).

Aminothiophen, thiophenine, $C_4H_3S.NH_2$, is a bright yellow oil. It resinifies on exposure to the air. Its HCl-salt consists of deliquescent needles. It does not yield a diazo-derivative. It combines with salts of diazobenzene, forming stable, mixed azo-dyestuffs—*e.g.*, $C_6H_5.N:N—C_4H_2S.NH_2.HCl$ (B. **18**, 2316).

Acetyl-amino-thiophen, $(C_4N_3S)NHCOCH_3$, is obtained from acetothienone oxime, $(C_4H_3S).C(NOH)CH_3$, by Beckmann's transformation (Ch. Ztg. **23**, 266). α-**Thienyl-urethane,** m.p. 48°, from α-thiophencarboxylic azide with alcohol, decomposes on saponification (J. pr. Ch. [2], **65**, 1).

5. *Sulphonic Acids.*—Like the benzene sulphonic acids, the thiophen sulpho-derivatives are produced by dissolving thiophen in sulphuric acid. In this reaction the thiophen must be diluted with petroleum ether, benzene, or some other agent. They can also be prepared from the thienyl-ketones by displacing the ketone groups by sulpho-residues (B. **19**, 674, 1620, 2623; **29**, 2562).

6. *Hydroxythiophens.*—**Hydroxythiophen** is not known. α-**Hydroxy-α_1-methyl-thiophen,** $C_4H_2(CH_3)S.OH$, is synthetically prepared from lævulinic acid. α-**Thienylsulphydrate,** $C_4H_3S.SH$, is prepared by reducing α-thiophen-sulphonic chloride, $C_4H_3S.SO_2Cl$. It is present in the crude thiophen product obtained by distilling succinic acid with P_2S_5. It boils about 166°.

7. *Alcohols.*—**Tertiary** α-**thienyl carbinols** $(C_4H_3S)C(OH)R_2$, like **dimethyl-, methyl phenyl-,** and **diphenyl-α-thienyl carbinol,** m.p. 33°, 50°, and 125°, have been obtained by the reaction of α-thienyl magnesium iodide with ketones (C. 1908, I. 1784).

8. *Aldehydes and Ketones.*—α-**Thiophenaldehyde,** $C_4H_3S.CHO$, results from the distillation of thienylglyoxylic acid. It boils at 198°. See B. **24**, 47; **25**, 2588, for the thiophene aldoximes.

If oxidized, even in the air, it forms α-thiophenic acid. Aqueous caustic potash converts it into thiophenic acid and thienylcarbinol: $2C_4H_3S.CHO + KOH = C_4H_3S.CO_2K + C_4H_3S.CH_2.OH$.

α-**Thienylcarbinol** is an aromatic liquid boiling at 207°.

Thiophenaldehyde condenses with sodium acetate and acetic anhydride to *thienylacrylic acid,* $C_4H_3S.CH:CH.COOH$, melting at 138°. This acid corresponds to cinnamic acid.

The ketone derivatives of thiophen are obtained very easily by the action of acid chlorides upon thiophen in the presence of aluminium chloride.

α-**Thienyl methyl ketone,** $C_4H_3S.CO.CH_3$, *Acetothienone,* is an oil boiling at 213°. If it be oxidized with permanganate, it first forms **Thienyl-glyoxylic Acid,** $C_4H_3S.CO.CO_2H$, melting at 91°, and then α-thiophenic acid.

Compare B. **24,** 232, R. 627, 952, for the condensation products of acetothienone with oxalic ester. **Dithienyl ketone,** *Thienone,* $CO(C_4H_3S)_2$, melting at 88° and boiling at 326°, is obtained from thiophen and $COCl_2$. **Thienyl phenyl ketone,** $C_4H_3S.CO.C_6H_5$, melting at 55° and boiling at 360°, results from thiophen, benzoyl chloride, and Al_2Cl_6.

See B. **28,** 1804, for the brominated thiophen ketones.

9. *Thiophen Carboxylic Acids.* — Thiophen carboxylic acids are formed by methods which are perfectly analogous to those employed in the preparation of the aromatic acids:

(1) By the oxidation of the alkyl thiophens with a solution of alkaline potassium permanganate. α-Ethyl-thiophen first yields thienylglyoxylic acid, but this changes to thiophenic acid.

(2) By the action of chloroformic ester and sodium amalgam upon iod- or bromthiophen, or by the interaction of the same reagent and thiophen, or the latter, urea chloride, and Al_2Cl_6.

α-**Thiophencarboxylic acid** (*Thiophenic acid*), $C_4H_3S.CO_2H$, melting at 126° and boiling at 260°, is also formed upon heating mucic acid with barium sulphide; from α-iodo-thiophen with chloroformic ester and Na-amalgam; and by oxidizing aceto- or propiothienone with permanganate (J. pr. Ch. 2, **65,** 6).

Its *nitrile,* $C_4H_3S.CN$, is produced when α-thiophene sulphonic acid is distilled with KCN, or by the elimination of water from thiophen aldoxime (B. **25,** 1311).

Ethyl ester, b.p.$_{25}$ 115°; hydrazide, m.p 136°; azide, m.p. 37° (J. pr. Ch. [2], **65,** 1).

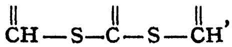
β-**Thiophencarboxylic acid** is produced when β-methylthiophen is oxidized. It melts at 136°.

2:3-**Thiophendicarboxylic acid,** $C_4H_2S.(CO_2H)_2$, melts at 260° with decomposition. Like phthalic acid, it forms a *fluoresceïn* with resorcinol.

The 2:4-*acid* melts at 118°. The 2:5-*acid* sublimes at 300°. Sodium amalgam reduces it to—

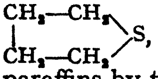
Tetrahydro-thiophendicarboxylic acid, $C_4H_6S(CO_2H)_2$, melting at 162°. This reduces ammoniacal silver solutions, especially upon warming. It resembles the hydrophthalic acids (B. **19,** 3274) in its entire behaviour.

Thiophentetracarboxylic methyl ester, $C_4(COOCH_3)_4S$, melting at 127°, is obtained when acetylenedicarboxylic methyl ester is heated with sulphur to 150°–155° in a sealed tube (B. **28,** 1635).

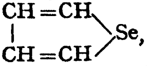
Thiophthen, 

$$\begin{array}{ccccc} CH & ——— & C & ——— & CH \\ \| & & \| & & \| \\ CH & —S— & C & —S— & CH \end{array}$$

, consists of two thiophen nuclei having two C-members in common. It boils at 225°. It results when citric acid is heated with P_2S_3 (B. **19,** 2444).

Tetrahydrothiophens are represented by tetramethylene sulphide,  $\left.\begin{array}{l}CH_2—CH_2\\ |\\ CH_2—CH_2\end{array}\right\rangle S$, and its homologues, obtained from $\alpha\delta$-dihalogen paraffins by the action of K_2S (B. **48,** 545, 3220).

3. SELENOPHEN.

The selenophens are constituted analogously to the thiophens. They contain an atom of selenium for sulphur. **Selenophen,**  $\left.\begin{array}{l}CH=CH\\ |\\ CH=CH\end{array}\right\rangle Se$, itself has not yet been prepared in a pure condition. It probably is formed when selenium ethide is conducted through tubes heated to redness (B. **18,** 1772).

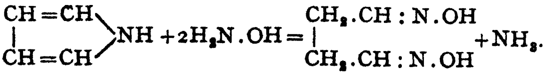
α,α_1-**Dimethylselenophen, selenoxen,** $C_4H_2(CH_3)_2Se$, boiling at 153°–155°, is produced when acetonylacetone is heated with phosphorus selenide (B. **18,** 2255). Isatin and sulphuric acid colour it a carmine red. It also shows the *Laubenheimer reaction* (p. 22).

4. PYRROLE GROUP.*

In pyrrole, C_4H_5N, there is a four-membered carbon chain united to a ring by the bivalent imine group. It is, therefore, a secondary amine, and, like its derivatives, possesses a feeble basic nature, as it dissolves in dilute acids. The pyrrole bodies, on the other hand, show great similarity in their behaviour to the phenols; the imine hydrogen can be easily replaced by potassium. The great reactivity of the methine hydrogen in pyrrol is quite remarkable. It can be as readily, and in some instances more easily, replaced than the imine hydrogen by the most varied groups and atoms. The constitution of pyrrole and its relations to furan and thiophen are deduced from its analogous syntheses from the γ-dicarbonyl compounds.

The great reactivity of the methine hydrogens in pyrrole is remarkable. They can be replaced by the most diverse atoms and groups with the same facility as the imine hydrogens, or even more. The constitution of pyrrole and its relations to furan and thiophen result from the synthetic formations from γ-dicarbonyl compounds.

A rather remarkable occurrence is the reversal of these syntheses —*i.e.*, the decomposition of the pyrrole ring with elimination of the imine group. This is induced by the action of hydroxylamine. Dioximes are thus produced. Thus, pyrrole yields succindialdoxime B. **22,** 1968):



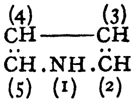
$$\left.\begin{array}{l}CH=CH\\ |\\ CH=CH\end{array}\right\rangle NH + 2H_2N.OH = \begin{array}{l}CH_2.CH:N.OH\\ |\\ CH_2.CH:N.OH\end{array} + NH_3.$$

The homologous pyrroles—*e.g.*, α-methylpyrrole, β-*iso*propyl, etc. —react similarly. This decomposition can be applied in determining the position of the substituents in the homologous pyrrols, as the α-alkyl pyrroles yield the oximes of ketones, while aldoximes are

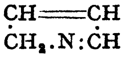
* Ciamician, " Il Pirrolo ed i suoi derivati," Roma, 1888.

obtained from the β-derivatives. These can be readily converted into dibasic acids (B. **24**, R. 649, 830).

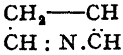
In contrast to furan and thiophen there is a possibility of a displacement of hydrogen in the formulation of pyrrole, so that, beside the normal Formula I., the desmotropic Formulæ II. and III. must be considered:

I.


$$\begin{array}{l} \overset{(4)}{\mathrm{CH}}\text{——}\overset{(3)}{\mathrm{CH}} \\ \underset{(5)}{\ddot{\mathrm{C}}\mathrm{H}}.\underset{(1)}{\mathrm{NH}}.\underset{(2)}{\ddot{\mathrm{C}}\mathrm{H}} \end{array}$$

II.


$$\begin{array}{l} \mathrm{CH{=\!=}CH} \\ \dot{\mathrm{C}}\mathrm{H_2.N{:}\dot{C}H} \end{array}$$

III.


$$\begin{array}{l} \mathrm{CH_2\text{——}CH} \\ \dot{\mathrm{C}}\mathrm{H : N.\dot{C}H} \end{array}$$

From Formula II. the pentachloro-pyrrole is no doubt derivable. The nitroso-, nitro-, and benzene-azo-pyrroles are possibly referable to the desmotropic Formulæ II. and III.

The position of the substituents in the methine groups of pyrrole is indicated, as in furan and thiophen, by numbers 2, 3, 4, 5, or letters α, α_1, β, β_1. Derivatives in which the imido-hydrogen atom is replaced are distinguished as *N*-derivatives, from the C-derivatives.

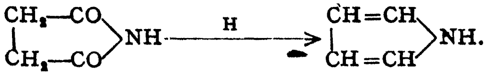
As the furan derivatives, on account of their relation to the hydrocarbons, so also the pyrroles and hydro-pyrroles possess physiological interest on account of their relation to albumen bodies, as exemplified by the formation of pyrrol derivatives from animal oil, glue, and the colouring matter of blood and leaves. They are also related to some alkaloids, such as those of coca and nicotine.

Pyrrole, boiling at 131°, with sp. gr. 0·9752 (12·5°), received its name from its property of imparting a fiery red (πυῤῥός) colour to a pine shaving moistened with hydrochloric acid. It was first found in coal-tar and bone oil (Runge, 1834; Anderson, 1858). It also is present in the distillation products of bituminous shales.

Bone oil, freed from the strongly basic substances (chiefly pyridine bases), consists of nitriles of the fatty acids, which are saponified upon boiling them with caustic potash, and in addition benzene hydrocarbons, pyrrole and its homologues. The pyrrole is contained in that portion of the oil boiling at 115°–130°, which is treated with metallic potassium, whereupon solid potassium-pyrrole separates.

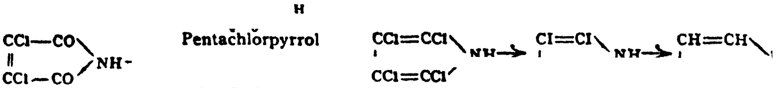
The oil obtained free from bone-glue by distillation is composed almost entirely of pyrrole compounds.

Pyrrole can be obtained synthetically (1) by the distillation of ammonium saccharate or mucate, or upon heating glycerol to 200°; (2) when acetylene and ammonia are conducted through tubes heated to redness: $2C_2H_2 + NH_3 = C_4H_4NH + H_2$; (3) from various acid imides and lactams, which may also be regarded as keto-derivatives of hydropyrroles. Thus, succinimide is reduced to pyrrole when it is distilled with zinc dust (or sodium):



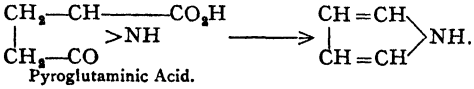
$$\begin{array}{l}\mathrm{CH_2{-}CO} \\ \mathrm{CH_2{-}CO}\end{array}\!\!\Big\rangle\mathrm{NH} \xrightarrow{\mathrm{H}} \begin{array}{l}\mathrm{CH{=}CH} \\ \mathrm{CH{=}CH}\end{array}\!\!\Big\rangle\mathrm{NH}.$$

Succinimide and dichloromaleïnimide, when heated with PCl_5, yield perchlorinated products, which, upon reduction, become tetrachlorpyrrole. The latter can be changed through tetraiodpyrrole into pyrrole:



Dichlormaleinimide Pentachlorpyrrol Hepta-chloride Tetrachlorpyrrol Iodol Pyrrol.

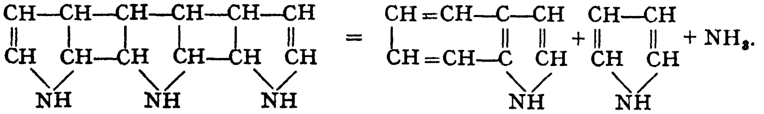
Pyrrole is also produced when pyroglutaminic acid (I. 559) is heated:



Pyroglutaminic Acid.

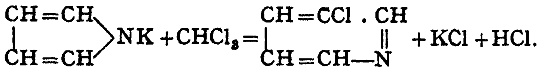
Pyrrole is a colourless liquid with an odour resembling that of chloroform. It becomes brown on exposure to the air. It is but slightly soluble in water, but dissolves very readily in alcohol and ether. It yields an indigo blue coloration with isatin and sulphuric acid, or with phenanthraquinone, etc. (B. **17,** 142, 1034; **19,** 106; **40,** 2492). Chromic acid oxidizes pyrrole to maleïnimide (C. 1904, II. 305). Pyrrole is a very feeble base. It is dissolved very slowly in the cold by dilute acids, but is rapidly resinified by strong acids. When its solutions in dilute acids are heated, ammonia is disengaged, and an amorphous red powder of varying composition is precipitated. This is *pyrrole red.*

The resinifying action of acids upon pyrroles is probably due to polymerization changes (B. **26,** 1711). Thus, dry hydrochloric acid gas precipitates $(C_4H_5N)_3HCl$ from the ethereal solution of pyrrole. This must be regarded as the salt of a polymeric tripyrrole, $(C_4H_5N)_3$. Crystalline **tripyrrole** is obtained by neutralizing the solution of pyrrole in dilute aqueous hydrochloric acid with ammonia, and then extracting with ether. Tripyrrole polymerizes further on standing, but when heated it breaks down into NH_3, indole, and pyrrole, according to the following equation (B. **27,** 476):



The transition of the pyrrole ring to that of pyridine is very remarkable.

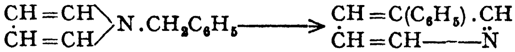
β-Chlorpyridine is formed upon heating potassium-pyrrole, or pyrrole and sodium alcoholate, with chloroform:



Bromo-pyridine.

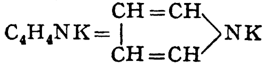
Similarly, bromoform yields β-brompyridine and methylene iodide. The homologous alkyl pyrroles, when heated alone to higher temperatures, also form pyridine derivatives.

It is probable that dichloro-methylpyrroles, $(C_4H_3N)CHCl_2$, occur as intermediate products, which, under the conditions of reaction, pass into chloropyridines. This is supported by the fact that, in some cases, pyrrole aldehydes are obtained (C. 1910, I. 654), thus resembling the action of chloroform and alkali upon phenols. A similar migration of the pyrrol nucleus into the pyridin nucleus takes place in conducting the vapours of N-alkyl- and *a*-alkyl pyrroles through incandescent tubes; here, also, the C-atom, newly entering the ring, takes up the *m*-position towards the N-atom. N-methylpyrrole yields pyridine, and N-benzylpyrrole, *β*-phenylpyridine (B. **38,** 1946).



$$\begin{matrix} CH=CH \\ CH=CH \end{matrix}\!\!>N.CH_2C_6H_5 \longrightarrow \begin{matrix} CH=C(C_6H_5).CH \\ CH=CH\text{——}N \end{matrix}$$

N-**Derivatives of Pyrrole.**—Potassium dissolves in pyrrole with an energetic evolution of hydrogen. It forms **Potassium-pyrrole,**



$C_4H_4NK = \begin{matrix} CH=CH \\ CH=CH \end{matrix}\!\!>NK$, a crystalline mass. This compound may also be obtained by boiling pyrrole with solid caustic potash. Water regenerates pyrrole and caustic potash. Sodium does not act like potassium.

A series of N-derivatives of pyrrole may be prepared from potassium-pyrrole. They are characterized by the fact that they change, on heating, to C-derivatives. This is analogous to the formation of homologous anilines from the alkyl anilines:

Alkyl iodides yield *N*-**Alkylpyrroles,** $C_4H_4 : NR$, which can be directly formed if in the pyrrole syntheses primary amines be substituted for ammonia, and also in the distillation of the alkylamine salts of mucic acid, etc.

N-**Methylpyrrole** boils at 113°. *N*-**Ethylpyrrole** boils at 131°. *N*-*Iso***amylpyrrole** boils at 180°–184°.

N-**Phenylpyrrole,** from aniline mucate, melts at 62°.

N,*β*-**Pyridylpyrrole,** $C_4H_4N.C_5H_4N$, boiling at 251°, is obtained from *β*-amino-pyridine mucate (B. **28,** 1907).

With acetyl chloride the product is: *N*-**Acetylpyrrole,** $C_4H_4N.CO.CH_3$, boiling at 178°. It is also produced (together with pyrryl methyl ketone) upon heating pyrrole with acetic anhydride.

Phosgene converts potassium-pyrrole into *N*-**carbonylpyrrole,** $CO<\begin{smallmatrix} N.C_4H_4 \\ N.C_4H_4 \end{smallmatrix}$, melting at 63° and distilling at 238°. When heated, it is converted into isomeric dipyrryl ketone, $CO<\begin{smallmatrix} C_4H_3.NH \\ C_4H_3.NH \end{smallmatrix}$.

N-**Pyrrolecarboxylic ester,** $C_4H_4N.CO_2.C_2H_5$, is formed when chlorcarbonic ester acts upon potassium-pyrrole. It is an oil boiling at 180°. It passes into **pyrryl carbamide,** $C_4H_4N.CO.NH_2$, if it is heated with aqueous ammonia.

N-**Cyano-pyrrole,** $C_4H_4N.CN$, is produced in the action of cyanogen chloride upon potassium-pyrrole. It rapidly polymerizes to a melamine derivative.

With benzoyl chloride, *N*-**benzoylpyrrole** is formed, $C_4H_4 : N.COC_6H_5$, b.p. 276°. It is converted by heating into *a*-pyrryl-phenyl ketone.

With Si-tetrachloride, **silico-tetrapyrrole**, $Si(NC_4H_4)_4$, is formed, colourless prisms, m.p. 173° (C. 1909, I. 1657).

Like aniline, pyrrole also reacts with methyl magnesium iodide, with production of methane and formation of a *pyrryl magnesium iodide*, $(C_4H_4N)MgI$, in which the Mg seems to be attached to the α-carbon atom, since with CO_2 it yields α-pyrrolecarboxylic acid; with acid chlorides, α-pyrryl ketone; and with oxalyl chloride, αα-dipyrroyl (B. **43**, 1012; C. 1911, I. 1548).

N-*Anilino*-derivatives of the pyrroles, $C_4R_4N.NHC_6H_5$, have been synthetically obtained from 1,4-diketo compounds and phenylhydrazine (compare A. **289**, 312).

C-Derivatives of Pyrrole.—1. **C-Alkylpyrroles**, *homologous pyrroles*, occur in bone oil. They are artificially produced:

(*a*) On conducting the vapours of pyrrole and alcohols over zinc dust.

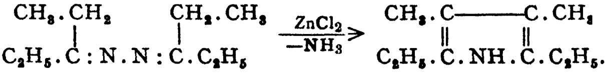
(*b*) Upon heating pyrrole or potassium-pyrrole with alkyl iodides. *N*-Alkylpyrroles result at first, but they immediately change to *C*-alkyl pyrroles.

(*c*) By splitting off carbon dioxide from the homologous pyrrole carboxylic acids.

(*d*) By direct synthesis from γ-diketones—*e.g.*, acetonyl acetone, etc.—upon heating with ammonia.

(*e*) On conducting N-alkylpyrroles through incandescent tubes (B. **37**, 2792).

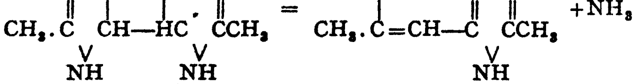
We must note the synthesis of $\beta\beta_1$-dimethyl-$\alpha\alpha_1$-diethylpyrrole on heating bis-diethyl azimethylene (diethyl ketazine, compare Vol. I.) with $ZnCl_2$ (B. **43**, 493):



$$\begin{matrix} CH_3.CH_2 & & CH_2.CH_3 \\ | & & | \\ C_2H_5.C & :N.N: & C.C_2H_5 \end{matrix} \xrightarrow[-NH_3]{ZnCl_2} \begin{matrix} CH_3.C & \text{———} & C.CH_3 \\ \| & & \| \\ C_2H_5.C & .NH. & C.C_2H_5. \end{matrix}$$

This reaction is analogous to Fischer's indole synthesis.

Behaviour.—The C-alkylpyrroles yield the corresponding pyrrole carboxylic acids when they are fused with caustic potash, while acid oxidizers give imides of the maleïc acid series or their monoximes (C. 1903, I. 838; B. **42**, 4964). Like pyrrole itself, they are readily resinified by acids. Gaseous hydrogen chloride precipitates compounds like $[C_4H_3(CH_3)NH]_2HCl$, $[C_4H_2(CH_3)_2NH]_2HCl$, from the ethereal solutions of the mono- and α,β-dialkylpyrroles. In aqueous solution dilute sulphuric acid changes these salts, with the elimination of ammonia, into alkylindoles. The reaction completes itself by the assumption of a structure for polymeric alkyl pyrroles similar to that attributed to tripyrrole (B. **24**, 2562; **26**, 1711):



Tetramethyle Dipyrrole

Tetramethyl Indole.

α-**Methylpyrrole** boils at 148°, while the β-variety boils at 143°.

α,β-**Dimethylpyrrole** boils at 165°. These three have been obtained from bone oil. α,α_1-**Dimethylpyrrole,** boiling at 165°, and α,β_1-**Dimethyl-**

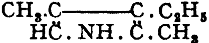
pyrrole, boiling at 160°, have been prepared from their dicarboxylic acids.

$\alpha\alpha_1$-Dimethylpyrrole is split up by the action of nitrous acid to the dioxime of dimethyltetraketone: $CH_3CO.C(NOH).C(NOH).COCH_3$; while $\alpha\beta_1$-dimethylpyrrole is oxidized by chromic or nitrous acid to citraconimide or its monoxime (C. 1903, I. 838; B. **42,** 4694).

α-**Ethylpyrrole,** boiling at 165°, and α-*iso***Propylpyrrole,** boiling at 175°, are produced in the action of aldehyde or acetone and zinc chloride upon pyrrole. See B. **30,** 434, for α,α_1-**Methyl***iso***propylpyrrole.**

$\alpha\alpha_1\beta$-**Trimethyl-pyrrole,** b.p. 180°, from its carboxylic acid (B. **38,** 1130). β,β_1-**Dimethyl**-α,α_1-**diethyl-pyrrole,** b.p.$_{55}$ 134° (see above).

Hæmopyrrole, *α,β_1-Dimethyl-β-ethylpyrrole* (?)



$$\begin{array}{l} CH_3.C\text{———}C.C_2H_5 \\ \quad HC.NH.C.CH_3 \end{array}$$

(?), b.p. 198°, is a very important compound in biochemistry. It is formed besides an isomeric dimethylethylpyrrole (*iso*hæmopyrrole) and the so-called phyllopyrrole, a trimethylpyrrole, by reduction from *Hæmin* (Nencki and Zaleski, B. **34,** 997), or better, from *Hæmatoporphyrin,* two disintegration products of hæmoglobin (A. **366,** 250), and from various derivatives of chlorophyll (A. **385,** 188); it is also formed by reduction from *Bilirubin,* a bile dye (C. 1905, I. 1254). During oxidation with nitrous acid, hæmo-pyrrole eliminates the methyl group standing in the α-position, and forms methyl-ethyl-maleïn-imide or its monoxime (B. **42,** 4693). By recently elaborated synthesis of $\alpha\beta_1$-dimethyl-β-ethylpyrrole, which is identical neither with hæmopyrrole nor with *iso*hæmopyrrole, the constitution of hæmopyrrole and its connections has again become uncertain (B. **44,** 3707).

α-**Phenylpyrrole,** melting at 129° and boiling at 272°, is formed by the rearrangement of *N*-phenylpyrrole upon the application of heat (B. **28,** 1905).

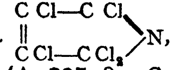
α,α_1-**Methylphenylpyrrole** melts at 101°.

Tetraphenylpyrrole, from $\alpha\alpha^1$-dibenzoyldibenzyl with ammonia, melts at 211° (B. **22,** 553).

α,β-**Pyridylpyrrole,** melting at 72°, is formed by the rearrangement of *N*,β-pyridylpyrrole. The methyl iodide of its *N*-methyl ether appears to be identical with nicotyrine iodmethylate obtained from nicotine (*q.v.*) (B. **28,** 1912).

With aromatic aldehydes the lower pyrroles react very violently, with resinification and dye formation; the higher ones partly give $ArCH(Pyrr)_2$ (B. **35,** 1647).

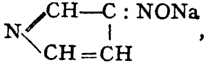
2. *Halogen Substitution Products.*—The halogens react very energetically with the pyrrole compounds. To prevent the formation of tar it is necessary to operate with very dilute solutions. Even then, as a rule, all the available hydrogen atoms of the pyrrole nucleus will be immediately replaced. Chlorine and bromine oxidize pyrrole in alkaline solution at once, and convert it into dichlor- or dibrom-maleïnimides.

In the action of sulphuryl chloride, SO_2Cl_2 (1, 2, and 3 mol.) upon ether solution of pyrrole, α-mono-, $\alpha\alpha_1$-di-, and $\alpha\alpha_1\beta$-trichloro-pyrroles are first formed as very unstable liquids; with 4 mol. SO_2Cl_2 tetrachloropyrrole is formed, and further action also replaces the fifth H-atom; pentachloropyrrole is formed, which was also obtained from succinimide and dichloro-maleïnimide with PCl_5, and yields dichloro-maleïnimide again on boiling with water. Pentachloropyrrole therefore has the formula  $\begin{matrix} CCl—CCl \\ \| \\ CCl—CCl_2 \end{matrix} \!\!>\!N$, and is derivable from the desmotropic Formula II. (A. **295,** 82; C. 1902, II. 522, 901).

Tetrachlorpyrrole, C_4Cl_4NH, melting with decomposition at 110°, is also obtained by the reduction of the product resulting from the action of PCl_5 upon succinimide and dichlormaleïnimide—the so-called pyrrole pentachloride, C_4Cl_5N, and the heptachloride, C_4Cl_7N (I. 463). It decomposes very rapidly *spontaneously*, and cannot be directly converted into pyrrole by a reverse substitution. Potassium iodide converts it into iodol (B. **19,** 3027).

α-Chloro-$\alpha_1\beta\beta_1$-tribromopyrrole, C_4ClBr_3NH, m.p. 96°–100°, and **$\alpha\alpha_1$-dichloro-$\beta\beta_1$-dibromopyrrole,** $C_4Cl_2Br_2NH$, m.p. 100°, from pyrrole by successive action of SO_2Cl_2 and Br; their N-methyl compounds, m.p. 120° and 126°, give on oxidation with HNO_3, dibromo-maleïc methyl imide, which settles their constitution as well as that of chloropyrrole (C. 1905, II. 828). $\alpha\alpha_1\beta$-Trichloro-β-bromo-pyrrole (see C. 1904, II. 994). **Tetrabromopyrrole** (compare C. 1901, I. 1323).

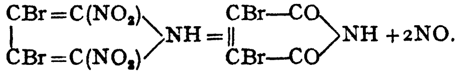
Iodol, Tetraiodopyrrole, C_4I_4NH, melting at 104° with decomposition, crystallizes in yellowish-brown needles. It is best made by the action of iodine upon pyrrole in the presence of alkalies. It is odourless. It is applied as an antiseptic, having the same action as iodoform (B. **20,** R. 220).

3. *Nitroso- and Nitro-pyrroles.*—Since pyrrole and its homologues are easily resinified by acids, these compounds can only be obtained indirectly, and are easily decomposed. Under the action of amyl nitrite and Na ethylate, pyrrole and its homologues with a free CH group in the β-position give Na salts of β-*iso*-nitroso-pyrroles,  $N\!\!<\!\begin{matrix} CH—C:NONa \\ | \\ CH=CH \end{matrix}$, derivable from the desmotropic Formula III. of pyrrole.

Sodium *iso*nitrosopyrrole, $(C_4H_3N):NONa$, **$\alpha\beta_1$- and $\alpha\alpha_1$-sodium dimethyl *iso*nitrosopyrrole** (see C. 1901, II. 778; 1902, II. 704; 1904, I. 1150; 1905, II. 626).

Nitropyrrole, $(C_4H_4N)NO_2$, light yellow rhombohedra, m.p. 63°. Its sodium salt, $(C_4H_3N):NOONa$ (?), is obtained from pyrrole and ethyl nitrate. **Nitro-$\alpha\beta_1$-dimethylpyrrole,** m.p. 111° (C. 1911, I. 1420).

Dinitropyrrole, $C_4H_2(NO_2)_2H_2NH$, melting at 152°, is obtained from pyrryl methyl ketone. **Dinitrodibromopyrrole,** $C_4Br_2(NO_2)_2NH$, is formed from dibromopyrrole dicarboxylic acid. It decomposes very readily with liberation of NO into dibrommaleïnimide:



$$\begin{matrix} CBr=C(NO_2) \\ | \\ CBr=C(NO_2) \end{matrix}\!\!>\!NH = \begin{matrix} CBr—CO \\ \| \\ CBr—CO \end{matrix}\!\!>\!NH + 2NO.$$

Nitrotriiodopyrrole, $C(NO_2)I_3NH$, and **dinitrodiiodopyrrole,** gold-yellow needles forming salts with alkalies, from iodol with fuming HNO_3 in acetic acid (C. 1901, I. 946).

4. *Amino- and Diazo-pyrroles.*—Hitherto only the β-amino-$\alpha\alpha_1$-diphenyl- and $\alpha\alpha_1\beta_1$-triphenyl-pyrroles, m.p. 188° and 184°, have been prepared. With HNO_2 they yield stable red-brown diazo-pyrroles, m.p. 123° and 159° (C. 1905, II. 900).

5. *Pyrrole-azo-compounds.*—**Azo-** and **Disazo-**compounds, perfectly analogous to the benzene azo-dyes, result from the interaction of benzene diazo-salts and pyrrole or homologous pyrroles. One and two molecules of the diazo-bodies enter the reaction (B. **19,** 2251):

$$(C_4H_3NH)N:NC_6H_5 \quad \text{and} \quad (C_4H_2NH){<}\begin{matrix}N:N.C_6H_5\\ N:N.C_6H_5\end{matrix}$$

Pyrroleazobenzene. Pyrroledisazobenzene.

6. *Pyrrole Aldehydes.*—**α-Pyrrolealdehyde** $(C_4H_3NH)CHO$, m.p. 45°, has been obtained by the action of chloroform and aqueous potash upon pyrrole. Oxime, m.p. 164°; phenyl hydrazone, m.p. 139°. Passes into α-pyrrolecarboxylic acid on oxidation (B. **33,** 536). **$\alpha\alpha_1$-Dimethyl-β-pyrrolealdehyde,** $(C_4H_2N)(CH_3)_2CHO$, m.p. 144° (C. 1910, I. 654).

7. *Pyrrole Ketones.*—These (together with the isomeric *N*-acetyl pyrroles) are produced by heating the pyrroles with acetic anhydride, and are also prepared by a *molecular* rearrangement of the *N*-acetyl pyrroles on being heated.

Potassium permanganate oxidizes the C-acetyl pyrroles to pyrroleglyoxylic acids, which molten caustic potash converts into pyrrolecarboxylic acids. The former condense with benzaldehyde to *cinnamoylpyrroles*—*e.g.*, $C_4H_3NH.CO.CH:CHC_6H_5$. The latter serve to characterize the acyl pyrroles.

α-Pyrryl methyl ketone, $C_4H_3(CO.CH_3)NH$, melts at 90° and boils about 220°. Its **oxime** melts at 146°. Potassium permanganate oxidizes it to **pyrrylglyoxylic acid,** $C_4H_3(NH).CO.CO_2H$, melting at 15°.

α-Pyrryl ethyl ketone, $C_4H_3NH.COC_2H_5$, m.p. 112°. **α-Pyrryl phenyl ketone,** $C_4H_3NH.COC_6H_5$, m.p. 78°.

Pyrryl dimethyl diketone, $C_4H_2(CO.CH_3)_2NH$, melts at 162°. Potassium permanganate oxidizes it to **pyrrole carboxylicglyoxylic acid,** $C_4H_2NH(COOH)CO.COOH$.

Dipyrryl ketone, $CO(C_4H_3.NH)_2$, melting at 100°, is formed, together with ***N*-Pyrroylpyrrole,** $C_4H_4N.CO.C_4H_3NH$, melting at 63°, upon heating *N*-carbonylpyrrole.

$\alpha\alpha$-Dipyrroyl, $NHC_4H_3.CO.CO.C_4H_3NH$, yellow crystals, m.p. 200°, from pyrryl magnesium iodide and oxalyl chloride.

8. *Pyrrole Carboxylic Acids.*—These resemble the phenol carboxylic acids, and are produced by perfectly similar methods:

(1) By the oxidation of the homologous pyrroles when fused with caustic potash.

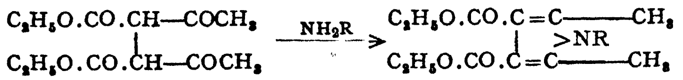
(2) By the action of carbon dioxide upon the potassium derivatives of the pyrroles:

$$C_4H_4NK + CO_2 = C_4H_3(NH).CO_2K.$$

(3) By the action of carbon tetrachloride and alcoholic potash upon pyrrole.

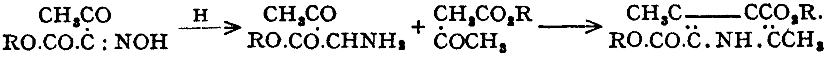
(4) The esters of the homologous pyrrole carboxylic acids may be synthesized by the action of alcoholic ammonia upon γ-diketocar-

boxylic and dicarboxylic esters. The ammonia can be replaced by primary amines, amino-acids, hydroxylamines, phenyl-hydrazine ($R = H, CH_3, OH, NHC_6H_5, CH_2COOH$, etc.):



$$\begin{array}{l}C_2H_5O.CO.CH{-}COCH_3\\ \qquad\qquad\quad |\\ C_2H_5O.CO.CH{-}COCH_3\end{array} \xrightarrow{NH_2R} \begin{array}{l}C_2H_5O.CO.C{=}C{-}CH_3\\ \qquad\qquad\quad |\;\; >NR\\ C_2H_5O.CO.C{=}C{-}CH_3\end{array}$$

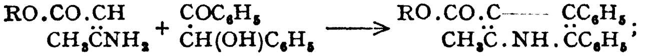
(5) By the reduction of a mixture of *iso*nitrosoacetoacetic ester with acetoacetic ester (similar reactions: B. **26**, R. 597; **27**, R. 586):



$$\begin{array}{l}CH_3CO\\ RO.CO.C:NOH\end{array} \xrightarrow{H} \begin{array}{l}CH_3CO\\ RO.CO.CHNH_2\end{array} + \begin{array}{l}CH_3CO_2R\\ COCH_3\end{array} \longrightarrow \begin{array}{l}CH_3C{-}{-}CCO_2R.\\ RO.CO.C.NH.CCH_3\end{array}$$

According to this method, numerous pyrrolecarboxylic acids and their pyrrole derivatives have been formed—*e.g.*, from *iso*nitroso-acetonedicarboxylic ester and acetonedicarboxylic ester: **Pyrrole-$\alpha\beta_1$-diacetic-$\alpha_1\beta$-dicarboxylic ester;** from *iso*nitroso- (or amino-) acetophenone and aceto-acetic ester: **$\alpha\beta_1$-Methylphenylpyrrole-β-carboxylic ester;** from *iso*nitroso- (or amino-) acetophenone and acetone dicarboxylic ester: **β_1-Phenylpyrrole-$\alpha\beta$-acetic-carboxylic ester;** from *iso*nitrosoacetylacetone and acetylacetone: **$\alpha\beta_1$-Dimethyl-$\alpha_1\beta$-diacetylpyrrole;** from *iso*nitrosodesoxybenzoin and acetoacetic ester: **$\alpha\alpha_1\beta_1$-Methyldiphenylpyrrole-β-carboxylic ester,** etc. (B. **35**, 2998).

(5*b*) Similar to this method is the formation of pyrrolecarboxylic acids from β-aminocrotonic acid with α-ketols, or with α-diketones and a reducing agent:



$$\begin{array}{l}RO.CO.CH\\ \quad CH_3CNH_2\end{array} + \begin{array}{l}COC_6H_5\\ CH(OH)C_6H_5\end{array} \longrightarrow \begin{array}{l}RO.CO.C{-}{-}CC_6H_5.\\ \quad CH_3C.NH.CC_6H_5\end{array}$$

from the condensation products of aminocrotonic ester with diketo-succinic ester we obtain by reduction with zinc dust **α-methylpyrrole-tricarboxylic ester** (B. **35**, 1545).

In the formation of pyrrolecarboxylic esters by condensation of α-chloroketones, acetoacetic ester, and ammonia (B. **23**, 1474), β-aminocrotonic ester also seems to occur as an intermediate product, and to react with the α-chloroketones in a manner similar to the α-ketols (B. **38**, 1125; compare also B. **44**, 493).

The pyrrolecarboxylic acids readily part with carbon dioxide upon the application of heat, and yield the corresponding pyrroles.

α-Pyrrolecarboxylic acid, $C_4H_3NH.COOH$, melting with decomposition at 192°, is obtained in the form of its *amide,* melting at 176°, together with pyrrole when ammonium mucate is heated.

Hydrazide, m.p. 232°; *azide,* $C_4H_3NH.CON_3$, is transformed by boiling with alcohol into **α-pyrrylurethane,** $(C_4H_3NH)NH.CO_2C_2H_5$, m.p. 56°, which, like the urethanes of amino-furan and -thiophen cannot be saponified to pyrryl amine (C. 1902, I. 1229).

A cyclic double acid amide of α-pyrrolecarboxylic acid is **Pyrocoll,** $CO{<}^{NC_4H_3}_{C_4H_3N}{>}CO$, melting at 268°. It is produced in the distillation of gelatin (κόλλα), and is artificially prepared by heating pyrrolecarboxylic acid with acetic anhydride. When it is heated with PCl_5, *perchlorpyrocoll,* $C_{10}Cl_8N_2O_2$, is produced. The latter absorbs eight additional chlorine atoms, and passes into the chloride, $(C_4Cl_7NCO)_2$, which becomes tetrachlorpyrrole upon reduction (p. 32).

β-Pyrrolecarboxylic acid, melting at 162°, is obtained by fusing methylpyrrole with caustic potash.

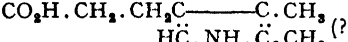
Methylpyrrolecarboxylic acids, $C_4H_2(CH_3)NH.COOH$. The α-acid melts at 169°; the β-acid at 142°. **α,α₁-Dimethylpyrrole-β-carboxylic acid,** $C_4H(CH_3)_2.NH.COOH$, melts at 118°. Its ester is derived from the corresponding dicarboxylic esters by the removal of carbon dioxide.

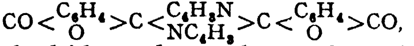
α,α₁-Diphenylpyrrolecarboxylic acid, $C_4H(C_6N_5)_2NH.COOH$, melting at 261°, is obtained from phenacylbenzoylacetic ester, $C_6H_5.CO.-CH(CO_2R)CH_2.CO.C_6H_5$ (p. 636). **α,α₁-Pyrroledicarboxylic acid,** $C_4H_2NH(COOH)_2$, from carboxypyrrylglyoxylic acid (p. 33), decomposes at 200° into carbon dioxide and pyrrole.

n-Phenylpyrrole-α-mono- and **αα₁-dicarboxylic acids** are formed on heating aniline mucate, and easily split off CO_2 (B. **35,** 2529).

α,α₁-Dimethyl-β,β₁-pyrroledicarboxylic acid, $C_4(CH_3)_2NH(COOH)_2$, from diacetosuccinic ester, breaks down at 251° into $2CO_2$ and α,α₁-dimethylpyrrole. **α,β₁-Dimethyl-β,α₁-pyrroledicarboxylic acid,** from acetoacetic ester with *iso*nitrosoacetoacetic ester, decomposes at 197° into $2CO_2$ and α,β₁-dimethylpyrrole. **αα₁-Diphenyl-ββ₁-pyrroledicarboxylic ester,** melting at 152°, is produced when ammonia acts upon dibenzoylsuccinic ester (A. **293,** 107).

αα₁-Methyl- and **αα₁-phenylpyrryl propionic acid** and **αα₁-pyrryl dipropionic acid,** from the fission product of furfural condensation products, acetonyl- and phenacyl-lævulinic acid and di-lævulinic acid with NH_3 (B. **35,** 2009).

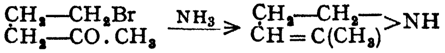
Phonopyrrolecarboxylic acid, *Hæmopyrrolecarboxylic acid, αβ-Dimethylpyrryl-β₁-propionic acid*  $\begin{matrix}CO_2H.CH_2.CH_2C & \text{———} & C.CH_3\\ & H\ddot{C}.NH.\ddot{C}.CH_3 & \end{matrix}$ (?), white needles, very easily oxidized, m.p. 125°. On treatment with HNO_2 it passes into the imide of the tribasic *hæmatinic acid* (Vol. I.) or its monoxime (A. **366,** 255; **377,** 316.)

Pyrrolene-phthalide,  $CO<\substack{C_6H_4\\O}>C<\substack{C_4H_3N\\NC_4H_3}>C<\substack{C_6H_4\\O}>CO$, is produced when phthalic anhydride and pyrrole are heated together (B. **19,** 2201). Its formula is probably analogous to that of pyrocoll.

Hydropyrrole Derivatives.—When pyrrole is reduced (zinc dust and acetic acid) two hydrogen atoms are added and dihydropyrrole or pyrroline, C_4H_7N, is produced. Further addition of hydrogen (by means of HI and phosphorus) leads to tetrahydropyrrole or pyrrolidine, C_4H_9N. The latter is formed direct by reduction of pyrrol with H and finely divided Ni (C. 1906, I. 1436). The nature of pyrrole is very essentially altered by this addition of hydrogen. Whereas pyrrole is a very feeble base, pyrroline and pyrrolidine, to even a greater degree, manifest the strong basic properties of the secondary amines of the aliphatic series.

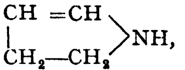
The addition of hydrogen probably occurs in the αα₁- or 2:5-position in the transformation of pyrroles into pyrrolines, similarly to other substances with conjugate ethylene linkages (B. **34,** 3954).

2:3-*Dihydropyrroles* have been obtained synthetically from the unstable γ-aminoketones and γ-bromoketones with NH_3 and primary amines:



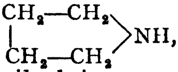
$$\begin{array}{l} CH_2-CH_2Br \\ CH_2-CO.CH_3 \end{array} \xrightarrow{NH_3} \begin{array}{l} CH_2-CH_2- \\ CH=C(CH_3) \end{array}\!\!>NH$$

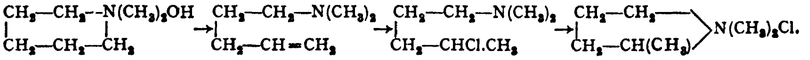
They are only distinguished from the 2:5-dihydropyrroles obtained in the reduction of pyrroles by the fact that they easily resinify in air, and are reduced to the corresponding pyrrolidines by tin and HCl alone. By treatment with benzoyl chloride and soda the 2:3-dihydropyrroles are easily split to γ-benzoylaminoketones. This splitting is especially easy in the case of the *N*-arylated-2:3-dihydropyrroles, which are only stable in the form of their salts (J. pr. Ch. [2], **75,** 329).

Pyrroline,  $\begin{array}{l} CH=CH \\ CH_2-CH_2 \end{array}\!\!>NH$, is a liquid that dissolves readily in water and boils at 91°. It has an alkaline reaction, smells like ammonia, and unites with acids to form salts. It is a secondary base. Nitrous acid converts it into a *nitrosamine*, $C_4H_6N(NO)$, melting at 38°.

Pyrroline and methyl iodide unite to dimethyl-pyrrolinium iodide, $C_4H_6N(CH_3)_2I$.

N-**Methylpyrroline,** $C_4H_6N.CH_3$, is formed by the reduction of methylpyrrole. It boils at 80°.

Pyrrolidine, Tetramethylene-imine,  $\begin{array}{l} CH_2-CH_2 \\ CH_2-CH_2 \end{array}\!\!>NH$, as well as its homologues, have already been described in connection with the aliphatic bodies. In addition to the methods there given for its production, another may be introduced at this point. It represents a transition of the six-membered piperidine ring into the five-membered pyrrolidine ring. Piperidine or pentamethylene-imine combines with alkyl iodides, forming dimethyl-piperidinium iodide, the hydroxide of which, upon distillation, changes to a compound with an open chain, Δ^δ. *pentenyldimethylamine.* The hydrochloride of the latter readily rearranges itself into the methochloride of *N*,α-dimethylpyrrolidine:



$$\begin{array}{l} CH_2-CH_2-N(CH_3)_2OH \\ CH_2-CH_2-CH_2 \end{array} \rightarrow \begin{array}{l} CH_2-CH_2-N(CH_3)_2 \\ CH_2-CH=CH_2 \end{array} \rightarrow \begin{array}{l} CH_2-CH_2-N(CH_3)_2 \\ CH_2-CHCl.CH_3 \end{array} \rightarrow \begin{array}{l} CH_2-CH_2- \\ CH_2-CH(CH_3) \end{array}\!\!>N(CH_3)_2Cl.$$

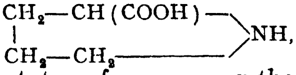
Other unsaturated amines analogous in constitution to Δ^δ-pentenyldimethylamine can be changed by HCl to pyrrolidine bases (Merling, A. **264,** 310; **278,** 1; compare B. **33,** 365). In a manner resembling the above conversion of piperidine, pyrrolidine is broken up by treatment with methyl iodide and distillation of the resulting dimethyl pyrrolidinium iodide with caustic potash. This gives Δ^γ-butenyldimethylamine and the methiodide of the latter, distilled with potash, gives trimethylamine and an unsaturated hydrocarbon, the so-called pyrrolylene, C_4H_6 (B. **19,** 569). Similarly, β-**methylpyrrolidine** (see Vol. I.) has been broken down to β-methyl divinyl or **isoprene** (C. 1898, I. 247); *N*-**benzoyl pyrrolidine,** b.p.$_{12}$ 191°, is split up by PCl_5 or PBr_5 to αδ-dichloro- and αδ-dibromobutane respectively (B. **39,** 1419):

$$(CH_2)_4N.COC_6H_5 \longrightarrow (CH_2)_4N.CCl_2C_6H_5 \longrightarrow Cl(CH_2)_4Cl + NC.C_6H_5,$$

Compare the action of PCl_5 upon dimethylbenzamide; also piperidine.

α-Methylpyrrolidine, b.p. 95°, from γ-amino-valerolactam by reduction with sodium and amyl alcohol, and from γ-methyl-dihydropyrrole with tin and HCl. On heating with zinc dust it yields α-methyl pyrrole (C. 1904, I. 42, 292). **$\alpha\beta_1$-Dimethylpyrrolidine,** b.p. 115°–117°; **αα,*N*-trimethylpyrrolidine,** b.p. 109°–113° (B. **34,** 3498). ***N*-Methyl pyrrolidine,** $(CH_2)_4NCH_3$, b.p. 79°, has been obtained from methyl-*n*-butylamine: $CH_3.CH_2.CH_2.CH_2NHCH_3$ by successive bromination with sodium hypobromite and splitting off of HBr by means of concentrated H_2SO_4 (B. **42,** 3427; **43,** 2035). It is also formed by the breaking up of the alkaloid nicotine (*q.v.*), an **α,2-pyridyl-*N*-methyl pyrrolidine,** with silver oxide (B. **38,** 1951), and by heating hygrinic acid (see below).

Proline, Pyrrolidine-α-carboxylic acid,

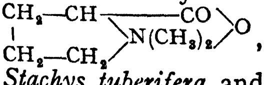


$$\begin{array}{l}CH_2—CH(COOH)—\diagdown \\ \mid \qquad\qquad\qquad\qquad\quad\ \ \rangle NH, \\ CH_2—CH_2————\diagup\end{array}$$

m.p. 203° (see Vol. I.), is found in its lævo-rotatory form among the hydrolytic decomposition products of numerous proteins—*e.g.*, *casein* (C. 1904, I. 293) and *gelatin* (B. **37,** 3071). Synthetically, *i*-proline, whose *m*-nitrobenzoyl compound has been split up into its optically active components by means of cinchonine (B. **42,** 2992), has been obtained from α,δ-dibromo-propylmalonic ester, $BrCH_2CH_2CH_2.CBr(CO_2R)_2$, with ammonia and subsequent saponification with HCl or baryta-water (A. **326,** 91); also from δ-bromo-α-amino-valerianic acid, the fission product of bromo-propyl-phthalimido-malonic ester (C. 1908, II. 806); and from δ-benzoyl-amino-α-bromovalerianic acid (B. **42,** 1022). We may note the conversion of pyro-glutaminic acid pyrrolidone-α-carboxylic acid, Vol. I.) into proline by reduction of its ester with Na and alcohol (B. **44,** 1332). A dipeptide (also obtained synthetically)—viz., ***l*-prolyl-*l*-phenyl-alanine,** $\overbrace{NH.CH_2.CH_2.CH}.$-$CONHCH(CO_2H)CH_2C_6H_5$—has been found among the hydrolytic fission products of gliadin (B. **42,** 4752). An **oxyproline,** $C_5H_9O_3N$, which on reduction with HI and P passes into proline, is found besides proline in the hydrolysis of numerous proteins (B. **41,** 1726).

***N*-Methyl-pyrrolidine-α-carboxylic acid,** *hygrinic acid,* m.p. 169°, is obtained by oxidizing *hygrin,* the alkaloid found in coca leaves; synthetically, it is formed similarly to proline (see above) from αδ-dibromopropylmalonic ester with methylamine (A. **326,** 91). Heat decomposes it into CO_2 and *N*-methylpyrrolidine (see above).

The methyl betaïne of hygrinic acid is **stachhydrine,**



$$\begin{array}{l}CH_2—CH———CO\diagdown \\ \mid \qquad\quad \diagdown N(CH_3)_2\diagup^{O} \\ CH_2—CH_2\diagup\end{array}$$

, which has been isolated from the bulbs of *Stachys tuberifera* and from the leaves of *Citrus aurantium* (B. **42,** 4654).

***N*-Methylpyrrolidine-$\alpha\alpha_1$-dicarboxylic acid,** m.p. 274° with dec., from αα′-dibromoadipinic ester with methylamine (B. **35,** 2065).

***N*-Methylpyrrolidine-$\alpha\alpha_1$-acetic-carboxylic acid** is identical with the tropinic acid formed by the oxidation of *tropine* and *ecgonine* (B. **31,** 1534; **32,** 1290).

$\alpha\alpha_1$-**Tetramethylpyrrolidine-β-carboxylic acid,** $\begin{array}{l}HOOCCH—C(CH_3)_2\\CH_2—C(CH_3)_2\end{array}\!\!>NH$, m.p. 220° with dec. The amide of this acid is formed from tetramethylpyrrolinecarboxylic amide by reduction with sodium amalgam. With KOBr the amide yields β-**aminotetramethylpyrrolidine,** b.p. 174°, a strong di-acid base. On splitting the ring by means of CH_3I the amide yields the open chain compound, $I(CH_3)_3N.C(CH_3)_2CH_2$-$C(CONH_2){:}C(CH_3)_2$; the free acid, even on heating only, splits off CO_2 and opens the ring, forming the compound, $H_2N.C(CH_3)_2.CH_2$-$.CH{:}\,C(CH_3)_2$ (B. **36,** 3351).

The lactams of the γ-amino-acids, like butyrolactam, α-**Pyrrolidone,** $\begin{array}{l}CH_2—CO\\CH_2—CH_2\end{array}\!\!>NH$, must be regarded as α-keto-pyrrolidines. These have already been described in Vol. I.

A β-keto-pyrrolidine is found in **tetramethyl-β-ketopyrrolidine,** $\begin{array}{l}CO—C(CH_3)_2\\CH_2—C(CH_3)_2\end{array}\!\!>NH$, b.p. 175°, obtained from tetramethyl-β-pyrroline carboxylic acid with Br and alkali, and shown to be a lower ring homologue of triacetoneamine. It has a decidedly basic character; its oxime, m.p. 172°, reduces to β-aminotetramethylpyrrolidine (A. **322,** 77).

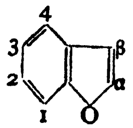
$\alpha\alpha_1$-Diketopyrrolidines are found in the imides of the succinic series, like succinimide $\begin{array}{l}CH_2—CO\\CH_2—CO\end{array}\!\!>NH$ (Vol. I.).

α,β-Diketopyrrolidines are produced by the reduction of the $\alpha\beta$-diketopyrrolines with Zn dust and acetic acid; also in the condensation of oxalacetic ester with aldehydes and ammonia or primary amines — *e.g.*, α,β-**diketo-α_1-phenyl-β_1-pyrrolidine carboxylic ester,** $HN\!\!<\!\!\begin{array}{l}CO—————CO\\ \quad\quad\quad\quad\quad\;\; |\\CH(C_6H_5)—CH(CO_2R)\end{array}$, melting at 185° (B. **30,** 602; C. 1907, II. 1787). **Xanthoxalanil,** $\begin{array}{l}CO—CO\\ |\\CH_2—CO\end{array}\!\!>N.C_6H_5$ (B. **24,** 1252), the anil of oxalacetic acid, is a triketo-pyrrolidine.

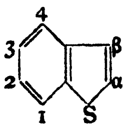
CONDENSED NUCLEI OF THE FURAN, THIOPHEN, AND PYRROLE GROUPS.

When two adjacent C-atoms of a furan, thiophen, or pyrrole nucleus participate in the formation of a benzene, naphthalene, etc., group, condensed nuclei result, which bear the same relations to the simple heterocyclic rings that the condensed nuclei of the naphthalene, phenanthrene, and anthracene groups bear to benzene.

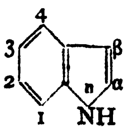
The following condensed nuclei are derived from furan, thiophen, and pyrrole:



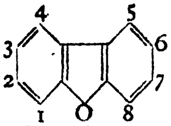
Benzofuran, Coumarone.



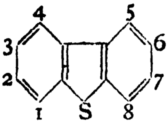
Benzothiophen.



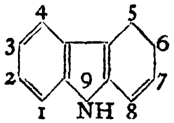
Benzopyrrole, Indole.



Dibenzofuran,
Diphenylene oxide.



Dibenzothiophen,
Diphenylene sulphide.



Dibenzopyrrole, Diphenylenimine,
Carbazole.

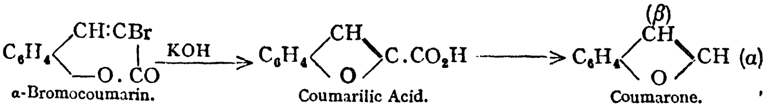
Condensed nuclei further are known in which two heterocyclic rings also participate in the formation of a benzene nucleus—*e.g.*, benzodifuran and benzodipyrrole derivatives.

Coumarone and *indole* should be especially mentioned as the parent substances of important groups. Indole is the mother substance of indigo. These two bodies will be considered together with benzothiophen. Next will follow the groups of dibenzo-compounds: diphenylene oxide, diphenylene sulphide, and carbazole.

5. BENZOFURAN OR COUMARONE GROUP.

The coumarone compounds, as their name would imply, are produced:

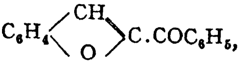
(1) By the action of alcoholic potash upon coumarin dibromides or α-brom-coumarins (Fittig, A. **216**, 162):



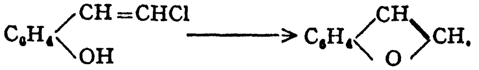
$$C_6H_4\left\langle\begin{matrix}CH{:}CBr\\ |\\ O.CO\end{matrix}\right. \xrightarrow{KOH} C_6H_4\left\langle\begin{matrix}CH\\ O\end{matrix}\right\rangle C.CO_2H \longrightarrow C_6H_4\left\langle\begin{matrix}\overset{(\beta)}{CH}\\ O\end{matrix}\right\rangle CH\ (\alpha)$$

α-Bromocoumarin. Coumarilic Acid. Coumarone.

Other coumarins react similarly—*e.g.*, umbelliferone, æsculetin, and daphnetin.

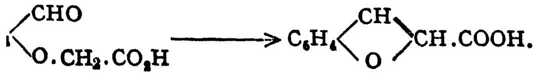
It is very certain that α-brom-*o*-hydroxycinnamic acid and its homologues occur as intermediate products. These split off HBr and form the coumarone ring. The formation of benzoylcoumarone,  $C_6H_4\left\langle\begin{matrix}CH\\ O\end{matrix}\right\rangle C.COC_6H_5$, from *o*-acetoxybenzalacetophenone dibromide and caustic potash, as well as by the condensation of salicylaldehyde and ω-bromacetophenone by means of caustic potash, proceeds analogously (B. **29**, 237, R. 290).

(2) Other *o*-disubstitution products of benzene combine to yield a coumarone ring. Caustic potash converts *o*-hydroxy-ω-chlorostyrene into coumarone (B. **26**, R. 678):



$$C_6H_4\left\langle\begin{matrix}CH{=}CHCl\\ OH\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH\\ O\end{matrix}\right\rangle CH.$$

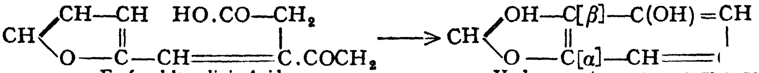
(3) By heating *o*-aldehydo-phenoxy-acetic acid with sodium acetate, coumarilic acid results (B. **17**, 3000):



$$\left\langle\begin{matrix}CHO\\ O.CH_2.CO_2H\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH\\ O\end{matrix}\right\rangle CH.COOH.$$

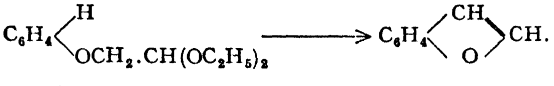
An analogous reaction is presented by the acetic-acid derivatives of *o*-hydroxyketones (B. **42,** 901).

(4) The synthesis of hydroxyacetocoumarone, however, from furfural-lævulinic acid represents a benzene ring formation (B. **26,** 345):



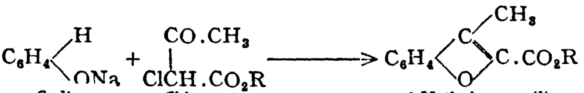
Furfural-lævulinic Acid. Hydroxyacetocoumarone, m.p. 190°.

(5) The action of zinc chloride in glacial acetic acid upon phenoxy-acetal produces coumarone:



By this method numerous alkylated coumarones are obtained by condensation of the homologues of phenoxy-acetal and of phenoxy-acetone, $C_6H_5.O.CH_2COCH_3$, and its homologues by means of sulphuric acid (A. **312,** 237).

(6) Just as the coumarins are formed from phenol and malic acid or acetoacetic ester, so the coumarones are obtained from the sodium salts of the phenols with α-chloracetoacetic ester (Hantzsch, B, **19,** 1291):



Sodium Phenate. α-Chloraceto-acetic Ester. β-Methylcoumarilic Ester.

Resorcinol and two molecules of the ester yield a *benzodifuran*, pyrogallol with three molecules of the ester form a *benzotrifuran*, while a *naphthofuran* is obtained from naphthol.

A perfectly similar reaction is noticeable in the production of coumarone and benzodifuran derivatives from quinones and chlorinated quinones—*e.g.*, chloranil, when heated with acetoacetic ester (J. pr. Ch. [2], **45,** 67; A. **283,** 245).

Coumarone, C_8H_6O, boiling at 177°, is formed by distilling coumarilic acid with lime. It is obtained from *o*-hydroxy-ω-chlorstyrene; from phenoxylacetal with zinc chloride (B. **30,** 1703), as well as from coal-tar, which also yields several methylcoumarones (B. **33,** 3014; C. 1907, I. 1426).

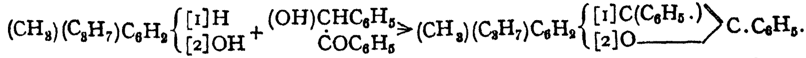
Coumarone polymerizes easily, especially under the influence of concentrated sulphuric acid, to so-called *coumarone resins*, which regenerate coumarone on dry distillation, with partial carbonization and formation of phenol. Similar behaviour is shown by the homologous coumarones (B. **33,** 2257, 3013). Heating with alcoholic potash to 200° splits up coumarone, forming *o*-ethylphenol and *o*-hydroxystyrene, as well as *o*-hydroxyphenyl acetic acid and *o*-hydroxyphenylethyl alcohol, and its anhydride, hydrocoumarone (B. **34,** 1806; **35,** 1630).

With chlorine and bromine, coumarone gives dihalogen addition products, $C_8H_6X_2O$, the dibromide melting at 86°. They easily pass into monochloro- and monobromo-coumarone. The monochlorocoumarone is probably a mixture of *α*- and *β*-chlorocoumarone, since on heating with alcoholic alkali to 180°–190° it yields, among other products, **β-keto-dihydro-coumarone,** $C_6H_4<\begin{matrix}CO\\O\end{matrix}>CH_2$, and **o-hydroxy-phenyl-acetic acid,** whose *lactone*, $C_6H_4\left\langle\begin{matrix}CH_2\\O\text{--}\end{matrix}\right\rangle CO$, yields with PCl_5, pure *α*-chlorocoumarone. On treating coumarone dichloride with sodium acetate, it splits up to form **o-hydroxy-mandelic aldehyde,** $C_6H_4\left\{\begin{matrix}[1]OH\\ [2]CH(OH)CHO\end{matrix}\right.$, m.p. 64° (A. **313,** 79). Heated by itself, coumarone dibromide gives exclusively **α-bromocoumarone,** liquid, b.p. 221°–223°, which is also formed from *o*-hydroxyphenylacetic acid lactone and $POBr_3$, and which splits up to *o*-hydroxyphenyl-acetic acid on heating with alcoholic potash. With alcoholic potash, on the other hand, coumarone dibromide yields chiefly **β-bromocoumarone,** m.p. 39°, b.p. 219°–220°, which on heating with alcoholic potash gives **β-ethoxycoumarone,** but also **α-ethoxy-coumarone** and *o*-oxyphenylacetic acid (B. **35,** 1633).

Nitrocoumarones.—If *α*-bromocoumarone is exposed to N_2O_3 vapour, bromine is liberated and **α-nitrocoumarone** is formed, m.p. 134°; it is also obtainable in small quantity by the nitration of coumarone; whereas *β*-bromocoumarone with N_2O_3 yields **α-nitro-β-bromocoumarone,** m.p. 132°. On treatment with Na ethylate solution, *α*-nitro-coumarone is changed into the monoxime of coumaranedione, $C_6H_4\left\{\begin{matrix}CH\\O\text{--}\end{matrix}\right\rangle CNO_2 \longrightarrow C_6H_4\left\{\begin{matrix}CO\\O\text{--}\end{matrix}\right\rangle C{:}NOH$. Compare the analogous transformations of 7-nitrostilbene, *α*- and *β*-nitronaphthalene, 9-nitro-phenanthrene, and 9-nitro-anthracene (B. **35,** 1633).

Numerous coumarones alkylated in the benzene nucleus and in the furan nucleus have been synthesized by the above method: **α-methyl coumarone,** b.p. 190°, from *α*-phenoxypropionic acetal; and **β-methyl coumarone,** b.p. 193°, from phenoxy-acetone, and from methylcoumarilic acid. Out of fifteen possible dimethyl coumarones, eleven are known: **αβ-dimethylcoumarone,** b.p. 210°, from dimethylcoumarilic acid. Others are two ethyl-, four trimethyl-, one *iso*propyl-, one tetramethyl-, and two methyl-*iso*propyl-coumarones, as well as an *α*- and a **β-naphtho-furan,** $C_{10}H_6\left\{\begin{matrix}[1]O\text{---}\\ [2]CH\end{matrix}\right\rangle CH$ and $C_{10}H_6\left\{\begin{matrix}[1]CH\\ [2]O\text{--}\end{matrix}\right\rangle CH$, m.p. 7° and 61° resp., b.p. 283° and 285° (A. **312,** 237). **α-Phenyl coumarone,** m.p. 121°, from sodium salicylaldehyde and phenyl chloro-acetic acid by method 3 (B. **36,** 3979).

β-Phenylcoumarone, two modifications, m.p. 13° and 42° resp., b.p.$_9$ 163°, from *o*-hydroxy-*as*-diphenylethylene by treating its dibromide with Na alcoholate (B. **36,** 4004). Both phenylcoumarones are also formed from *o*-hydroxy-diphenyl acetic acid lactone by heating with PBr_3 (B. **36,** 4006). *αβ*-Diphenyl coumarones—*e.g.*, **methyl-*iso*-propyl-diphenyl coumarone**—m.p. 116°, have been obtained by the condensation of phenols and benzoïn by means of sulphuric acid (C. 1899, II. 250):



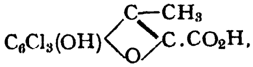
$$(CH_3)(C_3H_7)C_6H_2\left\{\begin{matrix}[1]H\\ [2]OH\end{matrix}\right. + \begin{matrix}(OH)CHC_6H_5\\ \dot{C}OC_6H_5\end{matrix} \Rightarrow (CH_3)(C_3H_7)C_6H_2\left\{\begin{matrix}[1]C(C_6H_5.)\\ [2]O\text{———}\end{matrix}\right\rangle C.C_6H_5.$$

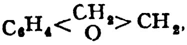
α-Acetylcoumarone, $C_8H_5O(COCH_3)$, m.p. 75°, is obtained from salicylaldehyde by means of chloracetone. With Br it gives a bromide, $C_8H_5O(COCH_2Br)$, which condenses with a second molecule of salicylaldehyde to **dicoumaryl ketone,** $(C_8H_5O)_2CO$, m.p. 154° (A. **312,** 333). Acetylcoumarone is reduced by Na and alcohol to hydrocoumarylmethylcarbinol and to ***O*-hydroxyphenyl-*sec*-butyl alcohol,** $HO.C_6H_4CH_2CH_2CH(OH)CH_3$ (B. **36,** 2863).

α-**Benzoylcoumarone,** $C_8H_5O(COC_6H_5)$, melting at 91°, obtained from *o*-acetoxybenzalacetophenone dibromide, as well as in the condensation of salicylaldehyde with phenacyl bromide, is decomposed by fusion with caustic potash into coumarone and benzoic acid (B. **29,** 237, R. 290).

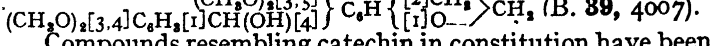
α-**Coumarilic acid,** $C_8H_5O.COOH$, melting at 190°, is obtained from *α*-bromocoumarin. Ester, amide, chloride, hydrazide, azide (see B. **34,** 773). The azide, with alcohol, gives coumaryl urethane, which on saponification splits up to *o*-hydroxyphenyl acetic acid.

β-**Methyl-*α*-coumarilic acid** melts at 189°. Its *ethyl ester* is produced on heating sodium phenoxide with acetoacetic ester (see above). It melts at 51°.

1,2,4-**Trichloro-3-oxy-*β*-methyl-coumarilic Acid,**  melting at 258°, is prepared from chloranil and acetoacetic ester.

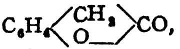
Hydrocoumarones.—**Dihydro-coumarone,** *coumaran,*  $C_6H_4<^{CH_2}_{O}>CH_2$, b.p. 189°, is formed with *o*-ethylphenol by reducing coumarone with sodium and alcohol (B. **25,** 2409). Synthetically, it is obtained from the HBr ester of *o*-hydroxyphenylethyl alcohol with soda, and from *o*-bromo-phenylbromethyl ether, $BrC_6H_4OCH_2CH_2Br$, with Na in ether. The latter method has also been used for forming *Bz*-**methylcoumarans** (B. **36,** 2873). *α*-**Phenylcoumaran,** $C_8H_7O(C_6H_5)$, m.p. 32°, from *α*-phenylcoumarone with Na and alcohol, together with *o*-hydroxydibenzyl. *β*-**Phenylcoumarane,** m.p. 38°, b.p.$_{14}$ 167°, from *α*-**chloro-*β*-phenylcoumarone,** $C_8H_4ClO(C_6H_5)$, the result of the action of PCl_5 upon *o*-hydroxydiphenylacetic acid lactone (B. **36,** 3992).

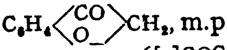
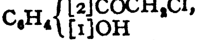
β-**Aminocoumaran,** $C_8H_7O.NH_2$, b.p.$_{18}$ 122°, by reduction of *β*-coumaranone oxime (B. **39,** 496). **Coumaran-*α*-carboxylic acid,** *hydrocoumarilic acid,* $C_8H_7O.CO_2H$, m.p. 116·5°, is obtained by reducing *α*-coumarilic acid with Na amalgam. A derivative of coumarane is probably represented by **catechin,** already mentioned in connection with tannins, for which the following constitution has been suggested:



$$(CH_3O)_2[3,4]C_6H_3[1]CH(OH)[4]\left.\begin{matrix}(CH_3O)_2[3,5]\\ \end{matrix}\right\} C_6H\left\{\begin{matrix}[2]CH_2\\ [1]O\text{—}\end{matrix}\right\rangle CH_2$$ (B. **39,** 4007).

Compounds resembling catechin in constitution have been obtained by the condensation of coumarane with benzoyl chloride and $AlCl_3$ and subsequent reduction with zinc dust and alkali (B. **41,** 1330; **42,** 911).

α-**Keto-dihydro-coumarone,** *α*-**coumaranone,**  $C_6H_4\langle^{CH_2}_{O}\rangle CO$, is probably represented by *o*-hydroxyphenylacetic acid lactone.

β-**Keto-dihydro-coumarone,** *β*-**coumaranone,**  $C_6H_4\langle^{CO}_{O}\rangle CH_2$, m.p. 97°, is obtained (1) from *o*-hydroxy-*ω*-chloracetophenone,  $C_6H_4\left\{\begin{matrix}[2]COCH_2Cl\\ [1]OH\end{matrix}\right.$, on heating with sodium acetate (B. **38,** 1081; **41,** 4273; **43,** 214); (2) by the condensation of phenoxy-acetic acid, $C_6H_5O.CH_2CO_2H$ with P_2O_5

(B. **38**, 3176); (3) from its carboxylic acid, whose ester, **β-coumaranone-α-carboxylic ester**, $C_6H_4<\substack{CO\\O}>CHCO_2C_2H_5$, m.p. 66°, is obtained by condensing phenoxy-acetic-*o*-carboxylic ester by means of sodium (B. **32**, 1867; C. 1900, I. 495; A. **312**, 258). 1-, 3-, and 4-**methyl-coumaranones**, $CH_3C_6H_3<\substack{CO\\O}>CH_2$, m.p. 102°, 85° and 54° respectively; 1,4-**dimethyl coumaranone**, m.p. 75°. *Bz*-**dihydroxy-coumaranone**, m.p. 226°, from pyrogallol and chloracetic acid with $POCl_3$ (B. **37**, 817).

Naphthocoumaranone, $C_{10}H_6(C_2H_2O_2)$, m.p. 92°, from 2-bromaceto-α-naphthyl acetate (B. **30**, 1468).

α-Mono- and **αα₁-dibromo-coumaranones**, m.p. 86° and 142°, are produced by brominating coumaranone.

α-Nitro-coumaranone is obtained in the form of its potassium salt, $C_6H_4<\substack{CO\\O}>C:NOOK$, from α-nitro-β-bromocoumarone by reaction with dialkylamines and heating the resulting compounds with alcoholic potash (B. **42**, 200); with benzaldehyde, coumaranone condenses to a benzylidene compound, m.p. 108°, with *p*-nitroso-dimethylaniline to a dimethyl anil of coumarandione (see below). Numerous substituted benzal coumarones have been obtained from substituted benzal-*o*-hydroxy-acetophenone dibromides (B. **31**, 699, 1759; **32**, 309, 2257). The dibromides of the benzal coumaranones are changed by dilute alkali into *flavonol* (B. **43**, 4233). On acylating coumaranones in alkaline solution we obtain **β-acyloxycoumarones**, $C_6H_4<\substack{C-OCOR\\O}>CH$; the isomeric *C-acyl compounds*, $C_6H_4<\substack{C(OH)\\O}>C.COR$, are obtained by the action of potassium carbonate upon **o-acyloxy-ω-chloraceto-phenones**, $C_6H_4<\substack{COCH_2Cl\\O.COR}$ (B. **43**, 2192).

Coumaranone dissolves in alkalies with formation of salts of β-oxycoumarone; in air, this solution rapidly takes a blood-red colour by simultaneous condensation and oxidation, the first product being a **keto-dihydro-bis-coumarone**, $C_6H_4<\substack{CO\\O}>CH-C<\substack{C_6H_4\\CH}>O$, which absorbs oxygen and easily passes into dioxy-bis-coumarone, $C_6H_4<\substack{C(OH)\\O}>C-C<\substack{C_6H_4\\C(OH)}>O$, m.p. 185°, orange-yellow needles. The latter, on further oxidation with H_2O_2, yields the oxygen analogue of Indirubin, the so-called **Oxindirubin**, $C_6H_4<\substack{CO\\O}>C:C<\substack{C_6H_4\\CO}>O$, m.p. 215°, orange-yellow needles subliming without decomposition, also obtained by condensation of β-coumaranone with coumarandione or hydroxyphenylglyoxylic acid with concentrated sulphuric acid (B. **43**, 212; **44**, 114).

Coumarandione,* $C_6H_4<\substack{CO\\O}>CO$, yellow plates, m.p. 134°, is the lactone of *o*-hydroxyphenylglyoxylic acid, from which it is obtained by heating with P_2O_5 in benzene solution or by vacuum distillation (B. **45**, 154). Coumarandiones alkylated in the benzene nucleus have been obtained from substituted *o*-hydroxyphenylglyoxylic acids by heating with P_2O_5 in benzene solution.

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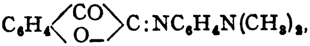
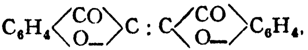
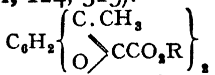
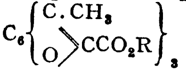
* The particulars concerning coumarandione given on p. 390, Vol. II., have turned out to be erroneous (see B. **45**, 162).

2- and 3-**Methylcoumarandiones,** m.p. 112° and 149° (see B. **42,** 234).

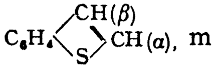
Coumarandione-α-*p*-dimethylaminoanil,  $C_6H_4\left<\begin{matrix}CO\\O\end{matrix}\right>C:NC_6H_4N(CH_3)_2$, from β-coumaranone and *p*-nitroso-dimethyl aniline, unites with 1 mol. β-coumaranone to form a compound, $C_{24}H_{20}O_4N_2$, m.p. 203° with dec., which is split up by HCl into *p*-amino-dimethylaniline and the oxygen analogue of indigo:

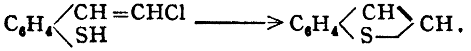
Oxindigo, αα-**bis-coumaran**-ββ-**dione,**  $C_6H_4\left<\begin{matrix}CO\\O\end{matrix}\right>C:C\left<\begin{matrix}CO\\O\end{matrix}\right>C_6H_4$, lemon-coloured prisms, m.p. 276°, subliming without dec. in the form of a yellow vapour. It is also formed from potassium α-nitrocoumarone on boiling with water or treating with Br or I (B. **44,** 124, 315).

Dimethyl-benzo-difuran-dicarboxylic ester,  $C_6H_2\left\{\begin{matrix}C.CH_3\\O\!>\!CCO_2R\end{matrix}\right\}_2$, from resorcinol and chloracetic acid ester, α-compound, m.p. 186°, β-compound, m.p. 141°. **Trimethyl-benzo-trifuran-tricarboxylic ester,**  $C_6\left\{\begin{matrix}C.CH_3\\O\!>\!CCO_2R\end{matrix}\right\}_3$ m.p. 297° with dec. From phloroglucinol and chloracetic ester.

6. BENZOTHIOPHEN OR THIONAPHTHEN GROUP.

The most important substances of this group have only recently become known through the investigations of P. Friedländer, who discovered in the sulphur analogue of indigo blue—viz., thio-indigo red and its derivatives—a class of commercially important vat dyes. The compounds of this group bear the same remarkable resemblance to the naphthalene derivatives as do the compounds of thiophen to the benzene derivatives.

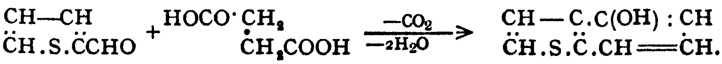
Thionaphthen, *Benzothiophen,*  $C_6H_4\left<\begin{matrix}CH(\beta)\\S\end{matrix}\right>CH(\alpha)$, m.p. 32°, b.p. 221° (C. 1897, II. 270) has an odour resembling naphthalene; it is formed like coumarone from o-hydroxy-ω-chlorostyrene (see above), through the *o*-sulphydryl-ω-chlorostyrene, which has only been isolated in the form of its xanthogenic ester (B. **26,** 2809):



$$C_6H_4\left<\begin{matrix}CH=CHCl\\SH\end{matrix}\right. \longrightarrow C_6H_4\left<\begin{matrix}CH\\S\end{matrix}\right>CH.$$

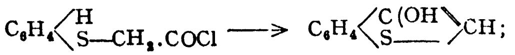
It is formed by reducing the easily accessible β-hydroxy-thionaphthen with zinc dust and glacial acetic acid (B. **41,** 230). It has also been found in tar from lignite (C. 1902, II. 804).

4-**Hydroxy-thionaphthen,** $C_8H_5(OH)S$, m.p. 72°, is formed by condensing thiophenaldehyde with succinic acid, as is acetoxycoumarone from the condensation of furfural and lævulinic acid (B. **19,** 1619):



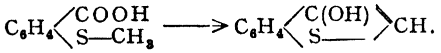
$$\begin{matrix}CH—CH\\ \ddot{C}H.S.\ddot{C}CHO\end{matrix} + \begin{matrix}HOCO\cdot CH_2\\ \dot{C}H_2COOH\end{matrix} \xrightarrow[-2H_2O]{-CO_2} \begin{matrix}CH—C.C(OH):CH\\ \ddot{C}H.S.\ddot{C}.CH=\!=\dot{C}H.\end{matrix}$$

β-Hydroxy-thionaphthen, *Thioindoxyl,* $C_6H_4\left\langle\begin{matrix}C(OH)\\S\end{matrix}\right\rangle CH$, m.p. 71°, colourless needles. Modes of preparation: (1) From β-hydroxy-thionaphthen-α-carboxylic acid, by elimination of CO_2 (A. **351,** 408); (2) from β-amino-thionaphthen or its carboxylic acid on boiling with dilute mineral acids; (3) from phenylthioglycollic acid by treating with fuming sulphuric acid or chlorosulphonic acid; but this last reaction is only suitable for forming substituted β-hydroxy-thionaphthens from those phenylthioglycollic acids in which sulphonation is excluded by the substituents present. A better method is (4) from phenylthioglycollic acid chloride and $AlCl_3$ (C. 1908, I. 1811):



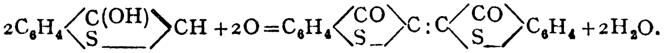
$$C_6H_4\left\langle\begin{matrix}H\\S-CH_2.COCl\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}C(OH)\\S\end{matrix}\right\rangle CH;$$

(5) from methyl-thiosalicylic acid on melting with caustic alkalies, best by adding a condensation agent like disodium cyanimide, lead sodium, etc. (C. 1908, II. 552):



$$C_6H_4\left\langle\begin{matrix}COOH\\S-CH_3\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}C(OH)\\S\end{matrix}\right\rangle CH.$$

β-Hydroxy-thionaphthen behaves like α-naphthol. It smells similarly, volatilizes in steam, and yields with diazonium salts, azo-dyes resembling the azo-derivatives of α-naphthol. In alkaline solution it oxidizes even in air, more easily with potassium ferricyanide, ferric chloride, etc., forming thio-indigo red:



$$2C_6H_4\left\langle\begin{matrix}C(OH)\\S\end{matrix}\right\rangle CH + 2O = C_6H_4\left\langle\begin{matrix}CO\\S\end{matrix}\right\rangle C:C\left\langle\begin{matrix}CO\\S\end{matrix}\right\rangle C_6H_4 + 2H_2O.$$

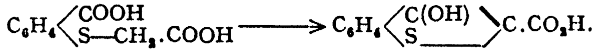
α-Bromo-β-hydroxy-thionaphthen, C_8H_5OSBr., m.p. 88°, and **α-dibromo-β-keto-dihydro-thionaphthen,** $C_8H_4OSBr_2$, m.p. 132°, by bromination of β-hydroxy-thionaphthen (B. **41,** 227). Both easily pass into thio-indigo red by splitting off HBr and Br_2 respectively (M. **29,** 371).

In many cases β-hydroxy-thionaphthen reacts in the desmotropic form as **β-keto-dihydro-thionaphthen,** $C_6H_4\left\langle\begin{matrix}CO\\S\end{matrix}\right\rangle CH_2$. Thus it yields with aldehydes and ketones coloured condensation products built like the indogenides (see below), and therefore called Thio-indogenides. The benzylidene compound, $C_6H_4\left\langle\begin{matrix}CO\\S\end{matrix}\right\rangle C:CHC_6H_5$, m.p. 127°, occurs in yellow needles (M. **30,** 347); with thionaphthenquinone, β-hydroxy-thionaphthen unites to form **thio-indirubin,** $C_6H_4\left\langle\begin{matrix}CO\\S\end{matrix}\right\rangle C:C\left\langle\begin{matrix}C_6H_4\\CO\end{matrix}\right\rangle S$; with isatin to form **thio-indigo scarlet,** $C_6H_4\left\langle\begin{matrix}CO\\S\end{matrix}\right\rangle C:C\left\langle\begin{matrix}C_6H_4\\CO\end{matrix}\right\rangle NH$; and with acenaphthenequinone to form the orange-coloured **α-thionaphthen acenaphthene indigo** or *ciba scarlet G,* $C_6H_4\left\langle\begin{matrix}CO\\S\end{matrix}\right\rangle C:C\left\langle\begin{matrix}CO\\C_{10}H_6\end{matrix}\right\rangle$ (B. **41,** 3331; M. **29,** 373).

With nitrous acid, β-hydroxy-thionaphthen yields **thionaphthenquinone-α-monoxime,** and with aromatic nitroso-compounds **thionaphthen-quinone-α-anils.**

α-Hydroxy-thionaphthen-β-aldehyde, $C_6H_4\langle^{C-CHO}_{S}\rangle C(OH)$, m.p. 130°, is formed on splitting up β-thionaphthene-α-indole indigo with alkalies (B. **41,** 1038).

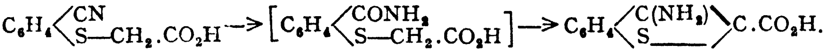
β-Hydroxy-thionaphthen-α-carboxylic acid, $C_6H_4\langle^{C(OH)}_{S}\rangle C.CO_2H$, methyl ester, m.p. 104°, is formed from *o*-carboxyphenylthioglycollic acid on melting with caustic alkalies or on heating with acetic anhydride and sodium acetate to 40° to 50° (A. **351,** 405):



$$C_6H_4\langle^{COOH}_{S-CH_2.COOH} \longrightarrow C_6H_4\langle^{C(OH)}_{S}\rangle C.CO_2H.$$

It easily splits up into CO_2 and β-hydroxy-thionaphthen, and therefore yields with aldehydes, HNO_2, etc., the same reaction products. Oxidation also yields thio-indigo red.

β-Amino-thionaphthen, $C_6H_4\langle^{C(NH_2)}_{S}\rangle CH$, oily, with an aceto-compound melting at 169°, smells like α-naphthylamine. It is formed by splitting off CO_2 from **β-amino-thionaphthen-α-carboxylic acid,** $C_8H_4S(NH_2)CO_2H$, m.p. 146°, without dec. The latter is obtained by saponifying *o*-cyanophenylthioglycollic acid by means of dilute alkalies or cold concentrated H_2SO_4:



$$C_6H_4\langle^{CN}_{S-CH_2.CO_2H} \longrightarrow \left[C_6H_4\langle^{CONH_2}_{S-CH_2.CO_2H}\right] \longrightarrow C_6H_4\langle^{C(NH_2)}_{S}\rangle C.CO_2H.$$

On heating with dilute mineral acids, β-amino-thionaphthen easily passes into β-hydroxy-thionaphthen (A. **351,** 412; C. 1908, I. 424).

Thionaphthenquinone, αβ-Diketo-dihydro-thionaphthen, $C_6H_4\langle^{CO}_{S}\rangle CO$, yellow prisms, m.p. 121°, b.p. 247°. (It should not be called "*thio-isatin*"; see *thio-isatin*, p. 63.) Preparation: (1) From thionaphthenquinone-α-anil (see below) by splitting up with dilute mineral acids (C. 1909, II. 1603; B. **43,** 1370); (2) from thionaphthen quinone-α-oxime (*iso*nitroso-thio-indoxyl) by hydrolysis with 50 per cent. H_2SO_4, or better by reducing to α-amino-β-hydroxy-thionaphthen and oxidizing with ferric chloride; (3) from the α-dibromo-β-keto-dihydrothionaphthen by boiling with water or lead acetate solution (B. **41,** 234; C. 1909, II. 767).

Thionaphthenquinone resembles isatin in its behaviour. Like the latter, it gives, with thiophen and concentrated H_2SO_4, a dark-blue coloration. With hydroxylamine and phenylhydrazine it reacts to form thionaphthenquinone β-oxime, $C_8H_4OS(:NOH)$, m.p. 186°, and thionaphthenquinone β-phenylhydrazone, $C_8H_4OS(:N.NHC_6H_5)$, m.p. 166°. No dioxime or diphenylhydrazone is formed. On the other hand, the **thionaphthenquinone α-oxime** or *isonitroso-thio-indoxyl*, $C_6H_4\langle^{CO}_{S}\rangle C:NOH$, m.p. 172° with dec., obtained from β-hydroxy-thionaphthen with HNO_2, yields with phenylhydrazine the thionaphthenquinone α-oxime β-phenylhydrazone, $C_8H_4S(:NOH)(:NNHC_6H_5)$, m.p. 154° (C. 1909, II. 1393).

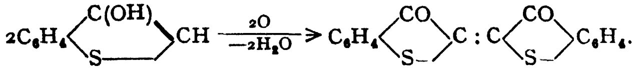
Thionaphthenquinone α-anil, $C_6H_4<\genfrac{}{}{0pt}{}{CO}{S}>C:NC_6H_5$, m.p. 151°, from α-dibromo-β-keto-dihydro-thionaphthen and aniline; the *p* mono-and dialkylamino-α-aniles of thionaphthenquinone have been obtained by the condensation of β-hydroxy-thionaphthen with *p*-nitrosoalkylanilines (B. **43**, 1370).

With β-hydroxy-thionaphthen, indoxyl, and similar compounds with reactive methylene groups, thionaphthenquinone unites with elimination of water to form indigoid dyes, the carbonyl in the β-position always coming into reaction. Thio-indirubin, *αβ-bisthionaphthen-βα-dione* $S<\genfrac{}{}{0pt}{}{C_6H_4}{CO}>C:C<\genfrac{}{}{0pt}{}{S}{CO}>C_6H_4$, red needles, m.p. 206° (M. **29**, 373), **β-Thio-naphthen-α-indole-αβ-dione,** $S<\genfrac{}{}{0pt}{}{C_6H_4}{CO}>C:C<\genfrac{}{}{0pt}{}{CO}{NH}>C_6H_4$.

The isomeric dyes are formed by the reaction of the same compounds with α-dibromo-β-keto-dihydro-thionaphthen or thionaphthen quinone-α-anils (see thio-indigo red).

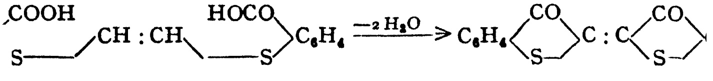
Thio-indigo red, $C_6H_4<\genfrac{}{}{0pt}{}{CO}{S}>C:C<\genfrac{}{}{0pt}{}{CO}{S}>C_6H_4$ (P. Friedländer, B. **39**), the sulphur analogue of indigo blue, is, like the latter, a vat dye, colouring the fibre in dull violet tones, and industrially valuable on account of its permanence. It crystallizes from nitrobenzene in brownish-red, shining needles, melting above 280°, and subliming even below that temperature. At higher temperatures it changes into an orange vapour and distils almost without decomposition. Its solutions show a strong yellowish-red fluorescence.

Modes of preparation (see Chem. Ind. **32**, 565): (1) By the oxidation of β-hydroxy-thiophenaphthen or its carboxylic acid in alkaline solution by atmospheric oxygen, or better by potassium ferricyanide, ferric chloride, etc.:



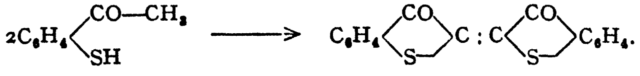
$$2C_6H_4\left<\begin{matrix}C(OH)\\S\end{matrix}\right>CH \xrightarrow[-2H_2O]{2O} C_6H_4\left<\begin{matrix}CO\\S\end{matrix}\right>C:C\left<\begin{matrix}CO\\S\end{matrix}\right>C_6H_4.$$

(2) By condensing the acetylenebis-thiosalicylic acid obtained from dichloroethylene and thiosalicylic acid by means of acid condensing agents such as chlorosulphonic acid (C. 1909, I. 605):



$$\begin{matrix}COOH\\S\end{matrix}\!\!\!>CH:CH<\!\!\!\begin{matrix}HOCO\\S\end{matrix}\!\!\!>C_6H_4 \xrightarrow{-2H_2O} C_6H_4\left<\begin{matrix}CO\\S\end{matrix}\right>C:C\left<\begin{matrix}CO\\S\end{matrix}\right>$$

(3) By oxidation of *o*-thiolacetophenone by atmospheric oxygen in alkaline solution (C. 1908, I. 2118):



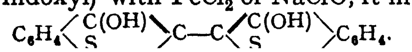
$$2C_6H_4\left<\begin{matrix}CO-CH_3\\SH\end{matrix}\right. \longrightarrow C_6H_4\left<\begin{matrix}CO\\S\end{matrix}\right>C:C\left<\begin{matrix}CO\\S\end{matrix}\right>C_6H_4.$$

This method is specially suitable for obtaining the industrially important alkoxy-derivatives of thio-indigo red (C. 1908, II. 1659).

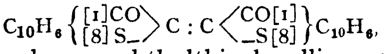
The following modes of preparation have only a theoretical interest:

(4) Treatment of thionaphthenquinone α-anil with CS_2 in acetic acid solution, with elimination of sulphur (M. **29**, 371).

(5) Condensation of α-dibromo-β-keto-dihydro-thionaphthen or thionaphthenquinone α-anil with β-hydroxy-thionaphthen.

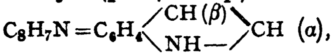
On treating thio-indigo red with zinc dust and alkali, or an alkaline hydrosulphite solution, we obtain a feebly yellow solution from which acids precipitate thio-indigo white, $C_{10}H_{10}O_2S_2$, insoluble in water, easily soluble in alkalies, and returning to thio-indigo red by oxidation in air. Since it is also obtainable by moderate oxidation of β-hydroxy-thionaphthen (thio-indoxyl) with $FeCl_2$ or NaClO, it must be regarded as **bis-thio-indoxyl**,  $C_6H_4{<}\begin{matrix}C(OH)\\S\end{matrix}{>}C{-}C{<}\begin{matrix}C(OH)\\S\end{matrix}{>}C_6H_4$. Its diacetyl compound melts at 240° (M. **29,** 372).

Numerous substitution products of thio-indigo red are technically important, especially the halogen, alkoxy- and alkyl thio-derivatives. It is found that substitution in the *p*-position to the carbonyl displaces the shade towards the yellow, while a substitution in the *p*-position to the S-atom displaces it towards the green (Ch. Ztg. **35,** 1159).

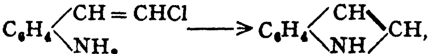
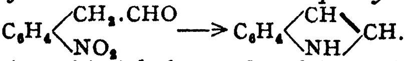
Peri - **Naphtho - thioindigo,**  $C_{10}H_6\left\{\begin{matrix}[1]CO\\ {[8]}S-\end{matrix}\right\rangle C:C\left\langle\begin{matrix}CO[1]\\ -S{[8]}\end{matrix}\right\}C_{10}H_6$, a blue-black powder, from *peri*-carboxynaphthylthioglycollic acid (C. 1908, I. 1815).

7. BENZOPYRROLE OR INDOLE GROUP.

The most important substances belonging in this group have been obtained from *indigo blue*, to which the indole derivatives bear an intimate kinship. Like the pyrroles, indole and its derivatives are of physiological importance as decomposition products of albumin. Indole, and especially the methylindoles, as derivatives of pyrrole, show most of the reactions of the latter (B. **19,** 2988). By a rupture of the ring the indole bodies are converted mainly into *ortho*amino-acids of benzene. Our knowledge of the constitution of indole and its derivatives, and their relations to indigo, is based chiefly upon the investigations of A. v. Baeyer (p. 64 *et seq.*).

Indole,  $C_8H_7N = C_6H_4{<}\begin{matrix}CH\,(\beta)\\NH\end{matrix}{>}CH$ (α), melting at 52° and boiling at 245° with decomposition, is contained in coal-tar, and can be liberated from the fraction distilling at 240°–260° (B. **43,** 3520). It is also obtained:

(1) By the distillation of oxygen-containing derivatives—*e.g.*, oxindole, indigo blue—with zinc dust; or, better, from indoxyl by reduction with Na-amalgam or zinc dust and alkali (B. **37,** 1134; C. 1904, II. 166; 1909, II. 31).

(2) By condensation of various *o*-amino-substitution products of benzene, or by the reduction of *o*-nitro-compounds; for example, the action of sodium alcoholate upon *o-aminochlorstyrene*,  $C_6H_4{<}\begin{matrix}CH=CHCl\\NH_2\end{matrix}\longrightarrow C_6H_4{<}\begin{matrix}CH\\NH\end{matrix}{>}CH$, analogous to coumarone (p. 39) and benzothiophen (p. 44); also by the reduction of *o-nitrophenylacetaldehyde* or *o-nitrocinnamic acid*,  $C_6H_4{<}\begin{matrix}CH_2.CHO\\NO_2\end{matrix}\longrightarrow C_6H_4{<}\begin{matrix}CH\\NH\end{matrix}{>}CH$. It is very probable that the production of indole from *phenylglycocoll*,

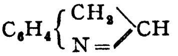
$C_6H_5NH.CH_2COOH$, and calcium formate proceeds in a similar manner (B. **23,** R. 654).

(3) The pyrogenic formation of indole from alkyl anilines, tetrahydroquinoline, and especially from *cumidine* when the vapours are conducted through tubes heated to redness, are due to ortho-condensations.

(4) Finally, indole is formed (together with skatole, *q.v.*) from *albuminates* in the pancreatic fermentation (method of production), or when they are fused with caustic potash. It is found in jasmine and other flowers.

Behaviour.—Indole crystallizes from water in shining leaflets. It possesses a peculiar odour, resembling that of naphthylamine, and is readily volatile in steam. Its vapour density (under diminished pressure) corresponds to the formula C_8H_7N. A pine splinter moistened with hydrochloric acid and dipped into its alcoholic solution or the vapours acquires a cherry-red colour. Indol possesses but very feeble basic properties (similar to pyrrole), and is easily resinified by acids. As in pyrrole, the imine hydrogen can be replaced by K or Na. Methyl Mg iodide converts it into indyl magnesium iodide (C. 1911, I. 1852).

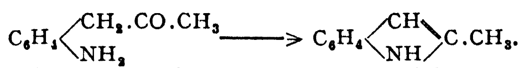
With picric acid it forms a compound which crystallizes in red needles (see also B. **32,** 2615; **39,** 2516).

The substituents of indole in the pyrrole ring are termed *N*-, *α*-, *β*-, or Py(1,2,3); those in the benzene ring, 1,2,3,4 or Bz(1,2,3,4) (A. **236,** 121) (see p. 38). Many indole derivatives are referable to a desmotropic form called **Indolenine,**  $C_6H_4\left\{\begin{matrix}CH_2\\N=\end{matrix}\right\}CH$ (C. 1908, II. 605).

N-*Nitrosoindole*, $C_7H_6N.NO$, melting at 172°, formed from indole and sodium nitrite, probably has the doubled formula (C. 1891, II. 62). Various *acetylindoles* are produced when indole and acetic anhydride are heated together (B. **23,** 1359, 2296).

Homologous Indoles are produced:

1. Like indole from *o*-amino-compounds of the benzene series by the formation of closed rings:



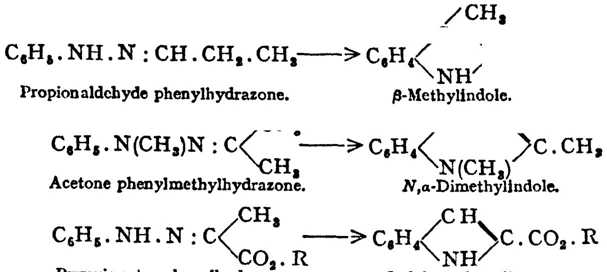
o-Aminobenzyl methyl ketone. *α*-Methylindole.

Similarly, *o*-amino-desoxybenzoin yields *α*-phenylindole, and *o*-methylamino-ω-chlorstyrene, *N*-methylindole.

2. By heating the anilines with compounds containing the group CO.CHCl. For example, aniline and chloracetone yield *α*-methyl indole; with *β*-bromolævulinic acid, *α,β*-dimethylindole is the product. A simultaneous evolution of CO_2 occurs here. This reaction is parallel to that of the so-called *quinaldine synthesis*. For its course see B. **25,** 2860; **26,** 1336, 2638; **37,** 867. Aniline and bromacetophenone yield *α*-phenylindole.

3. A noteworthy method for the production of the alkylindoles consists in condensing the phenylhydrazones of the aldehydes, ketones, and ketonic acids by heating them with hydrochloric acid or zinc

chloride (E. Fischer, B. **19,** 1563; **22,** R. 14), when ammonia is split off:

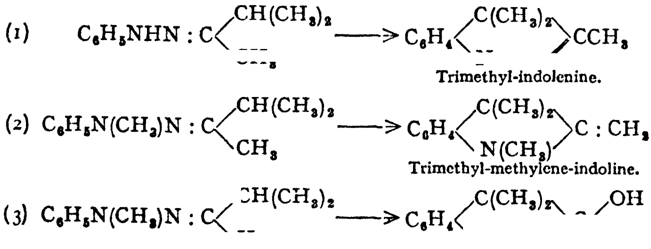


Propionaldehyde phenylhydrazone. β-Methylindole.

Acetone phenylmethylhydrazone. *N*,α-Dimethylindole.

Pyruvic ester phenylhydrazone. α-Indole carboxylic ester.

The *unsym.*-alkylphenylhydrazine derivatives react very easily with pyroracemic acid upon warming them with dilute hydrochloric acid, sulphuric or phosphoric acid; the products are N-alkylindolecarboxylic acids. The phenylhydrazones of the β-ketonic acids—*e.g.*, acetoacetic ester—are principally converted into pyrazole compounds. Some, when heated with concentrated sulphuric acid, yield indol compounds (B. **27,** R. 793). This is especially true of the *unsym.*-alkylphenylhydrazones. In aldehydes and ketones containing methine groups adjoining CO groups, the condensations usually take place in a modified manner, with expulsion of the tertiary H-atom. The phenylhydrazones yield *pseudo*-indole or indolenine derivatives; the *unsym.*-alkylphenylhydrazones give derivatives of a dihydroindole or indoline (B. **31,** 1488, 1948. M. **21,** 156; C. 1900, I. 867. See also Indolinones).



Trimethyl-indolenine.

Trimethyl-methylene-indoline.

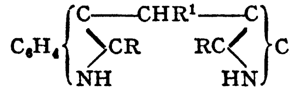
Trimethyl-indolinol.

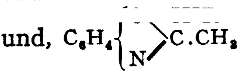
4. The polymeric alkylpyrroles, upon standing with dilute sulphuric acid, part with ammonia and pass into alkylindoles—*e.g.*, tetramethyldipyrrole changes to α,β,2,3-tetramethylindole.

5. On the formation of indoline or benzopyrrole derivatives from pyrroles with 1,4-diketones, see B. **35,** 2607; C. 1902, II. 1472; 1905, I. 1154.

Behaviour.—The alkylindoles substituted in the pyrrole nucleus possess generally a fæcal odour, and can be distilled without decomposition. The phenylindoles and indolecarboxylic acids are non-volatile and odourless. They are more stable towards acids than indole, dissolve in concentrated acids, and are reprecipitated unaltered by water. Picric acid unites with all of them, forming compounds crystallizing in red needles. Most of the indole derivatives give the pine-shaving reaction, the exceptions being the indolecarboxylic acids and the α,β-dialkylindoles. The alkylindoles, like the alkylpyrroles, yield indolecarboxylic acids when they are fused with caustic potash.

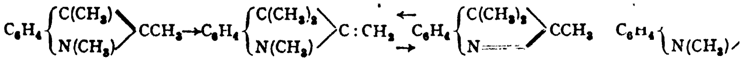
The indoles, like pyrrole, combine with nitrous acid, acid anhydrides, and diazo-compounds, hydrogen atoms of the pyrrole nucleus being replaced by the *iso*nitroso, the acidyl, benzene-azo group, etc.

With aldehydes (1 mol.), the α-substituted indoles condense with expulsion of the H-atom in the β-position to form compounds of the type,  $C_6H_4\left\{\begin{matrix}C\text{——}CHR^1\text{——}C\\ \quad >CR \qquad RC< \quad \\ NH \qquad\qquad HN\end{matrix}\right\}C_6H_4$ (B. **36,** 4326; **37,** 322, 1221; J. pr. Ch. [2], **61,** 249).

Oxidation converts these condensation products into dyes resembling fuchsin, so-called *Rosindoles,* which are also obtained direct by the condensation of the corresponding indoles with benzoyl chloride and $ZnCl_2$ (B. **20,** 815). The keto-group of the *p*-diamino-benzophenones also reacts like the aldehydes, forming red to violet dyes (C. 1902, I. 610). Methylindole unites with aldehydes in molecular proportion to the compound,  $C_6H_4\left\{\begin{matrix}\text{- -} \\ N\end{matrix}\right.>C.CH_3$ (B. **36,** 308; **38,** 2640). In this desmotropic form methylindole also reacts with aromatic nitroso-compounds (C. 1908, II. 650).

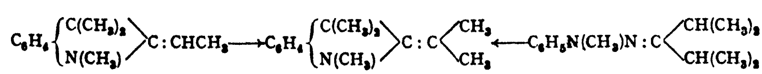
A peculiar behaviour is shown by indole and the alkylated indoles on thorough treatment with alkyl iodides. Thus, in the cases of indole and methylindole, treated with methyliodide, the methylation of the H-atoms of the pyrrole nucleus is followed by the addition of a further methyl group:

N$\beta\beta$-**Trimethyl-α-methyleneindoline** is formed, the constitution being proved by its synthesis, by its oxidation to trimethyl indolinone, and by its disintegration to form synthetic *trimethylindolenine,* from which latter it can be recovered by methylation (B, **31,** 1488; C. 1898, II. 542; 1899, I. 280):



$$C_6H_4\left\{\begin{matrix}C(CH_3)\\N(CH_3)\end{matrix}\right.>CCH_3 \rightarrow C_6H_4\left\{\begin{matrix}C(CH_3)_2\\N(CH_3)\end{matrix}\right.>C:CH_2 \underset{\rightarrow}{\leftarrow} C_6H_4\left\{\begin{matrix}C(CH_3)_2\\N\text{====}\end{matrix}\right.>CCH_3 \quad C_6H_4\left\{N(CH_3)\right.$$

Trimethylmethyleneindoline gives on further methylation *ethylidene-* and iso*propylidene-trimethyl-indoline,* also obtained synthetically from ethyl *iso*propyl ketone and di*iso*propyl ketone methylphenyl hydrazones by method 3:

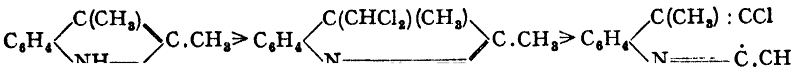


$$C_6H_4\left\{\begin{matrix}C(CH_3)_2\\N(CH_3)\end{matrix}\right.>C:CHCH_3 \longrightarrow C_6H_4\left\{\begin{matrix}C(CH_3)_2\\N(CH_3)\end{matrix}\right.>C:C<\begin{matrix}CH_3\\CH_3\end{matrix} \longleftarrow C_6H_5N(CH_3)N:C<\begin{matrix}CH(CH_3)_2\\CH(CH_3)_2\end{matrix}$$

Similar processes take place during the ethylation of methylated, ethylated, and phenylated indoles, in which isomerization has also been observed, due to migration of the alkyl groups (C. 1899, I. 282; 1900, I. 867; 1902, II. 1322).

On heating with chloroform and sodium alcoholate the alkylindoles, like pyrrole and indole, enlarge the ring and yield β-chloroquinolines and indole aldehydes.

αβ-Dimethylindole yields as a primary product β-**dichloromethyl-αβ-dimethyl-indolenine,** which, on heating with sodium ethylate, passes into β-**chloro-αγ-dimethylquinoline** (C. 1905, I. 1155):



$$C_6H_4\left\langle\begin{array}{l}C(CH_3)\\NH\end{array}\right\rangle C.CH_3 \rightarrow C_6H_4\left\langle\begin{array}{l}C(CHCl_2)(CH_3)\\N\end{array}\right\rangle C.CH_3 \rightarrow C_6H_4\left\langle\begin{array}{l}C(CH_3):CCl\\N=\!=\!=\!C.CH_3\end{array}\right.$$

N-**Methylindole,** $C_8H_6N(CH_3)$, boiling at 239°; *N*-**Ethylindole,** boiling at 247°; *N*-**Allylindole,** boiling at 252° (B. **26,** 2174); and *N*-**Phenylindole,** $C_8H_6N(C_6H_5)$, are obtained from their carboxylic acids by the elimination of carbon dioxide. Bromine in sodium hydroxide oxidizes *N*-methyl and *N*-ethyl indole to *methyl* and *ethyl-ψ-isatin.*

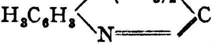
α-**Methylindole,** $C_8H_5(CH_3)NH$, *Methylketole,* arises from *o*-aminobenzyl methyl ketone, and acetone phenylhydrazone. Its odour is like that of indole, and its reactions are similar. M.p. 59°, b.p. 268°. Fused with caustic potash, it forms α-indolecarboxylic acid. By oxidation with $KMnO_4$ the indole ring is split and acetanthranilic acid is formed. Passed through incandescent tubes it is transposed into *quinoline* (B. **38,** 1949). With chloroform and sodium alcoholate it yields β-**chloro-quinaldine** (B. **21,** 1940).

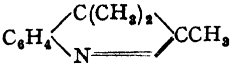
β-**Methylindole,** *Skatole,* $C_8H_5(CH_3)NH$, occurs in human fæces (with a little indole). It may be obtained, together with indole, from reduced indigo, by the putrefaction of albuminoids, or (with indole) in the fusion of the same with potassium hydroxide. It can be prepared without difficulty by heating propaldehyde-phenylhydrazone with zinc chloride. It melts at 95° and boils at 265°. It has a penetrating fæcal odour. With chloroform and Na alcoholate it yields β-**chlorolepidine** (B. **39,** 4388). β-Ethylindole, m.p. 43°, from indyl magnesium iodide and C_2H_5MgI. Also from *N*-butyraldehyde phenylhydrazone (C. 1905, II. 677).

αβ-**Dimethylindole,** m.p. 106°, from methyl ethyl ketone phenyl hydrazone (A. **236,** 128).

N,α,β-**Trimethylindole** boils at 280° (see above). α,β,2,3-**Tetramethylindole** melts with decomposition at 285° (B. **22,** 1924). It is obtained from tetramethyldipyrrole. α-**Phenylindole,** $C_8H_5(C_6H_5)NH$, melting at 187°, has been prepared from acetophenone phenylhydrazone, from *o*-nitrodesoxybenzoin, from bromacetophenone and aniline (see above), and, lastly, by the rearrangement of β-**Phenylindole,** $C_8H_5(C_6H_5)NH$, melting at 89°, upon heating it to 170° with zinc chloride (B. **21,** 1811). Similar rearrangements are manifested by the different *methylphenylindoles* (B. **22,** R. 44). α-**Thienylindole,** melting at 162°, and α-**Naphthylindole,** melting at 180°, are obtained from the phenylhydrazones of naphthyl and thienyl methyl ketones (B. **38,** 217).

αβ-**Naphthopyrrole,** $C_{10}H_6\left\{\begin{array}{l}[\alpha]CH\\ [\beta]NH\end{array}\right\rangle CH$, is obtained from its sulpho-acid (B. **31,** 251).

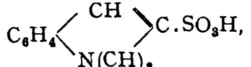
β,β,3-**Trimethyl-indolenine,**  $CH_3C_6H_3\left\langle\begin{array}{l}C(CH_3)_2\\N=\!=\!=\end{array}\right\rangle CH$, m.p. 143°, from *iso*butyraldehyde *p*-tolylhydrazone, is polymerized on standing. On boiling with HCl it transposes into α,β,3-trimethylindole, m.p. 190°

(M. **27**, 731). *α,β,β*-**Trimethylindolenine,**  $C_6H_4\left<\begin{matrix}C(CH_3)_2\\N=\!=\!=\end{matrix}\right>CCH_3$, m.p. 229° (C. 1899, II. 436), from methyl *iso*propyl ketone phenylhydrazone (see above); *α,β-dimethyl-β-ethyl-indolenine,* m.p. 243°, from *methyl ethyl ketone phenylhydrazone* (compare C. 1900, I. 867).

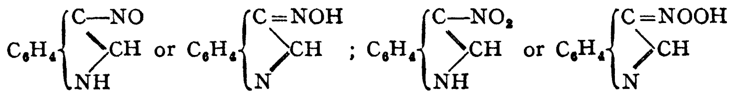
αα-Methyl-*ββ*-diethyl indolenine is obtained by the ethylation of methylindole (C. 1899, I. 280).

2. Chloro-substitution products of the indoles are formed by the action of sulphuryl chloride upon the ether solutions of indoles or from the oxygen derivatives, oxindole and dioxindole, with PCl_5. *α*-**Chlorindole,** C_8H_5ClNH, m.p. 91·5°, heated with mineral acids, easily passes into oxindole.

α,β-**Dichlorindole,** $C_8H_4Cl_2NH$, m.p. 104°. *α*-**Chloro-*β*-bromindole,** $C_8H_4ClBrNH$, m.p. 92° with dec. (C. 1905, II. 1346; 1906, I. 854). *β*-**Iodindole,** C_8H_5INH, m.p. 72° (see B. **41,** 4005). *β*-**Iodo-*α*-methylindole,** m.p. 82° (see C. 1909, II. 282).

3. Sulpho-acids of the indoles and naphthindoles, containing the sulpho-group in the pyrrole nucleus, have been prepared synthetically from methyl and ethyl aniline and from the naphthylamines by condensation with *glyoxal bisulphite* (B. **27,** 3258; **31,** 250; **41,** 1367); *N*-**methyl-indole-*α*-sulphonic acid,**  $C_6H_4\left<\begin{matrix}CH\\N(CH)_3\end{matrix}\right>C.SO_3H$, on boiling with HCl, splits off SO_2 and passes easily into *n*-methyl oxindole.

4. *Nitroso-, Nitro-,* and *Benzeneazo-Derivatives.*—With nitrous acid, obtained from sodium nitrite and glacial acetic acid or, better, amylnitrite and sodium alcoholate, and with nitric acid obtained from ethyl nitrate and sodium in ether, smooth reactions are only shown by those indoles in which the H-atom in the *β*-position is not substituted, like indole, methylindole, and *α*-phenylindole; the latter gives nitroso- and nitro-derivatives, which, however, also react in the tautomeric form of *iso*nitroso- and *iso*nitro-bodies (see the tautomerism of the nitrosophenols).

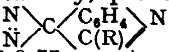


$$C_6H_4\left\{\begin{matrix}C—NO\\ \quad>CH\\NH\end{matrix}\right. \text{ or } C_6H_4\left\{\begin{matrix}C=NOH\\ \quad>CH\\N\end{matrix}\right. ;\ C_6H_4\left\{\begin{matrix}C—NO_2\\ \quad>CH\\NH\end{matrix}\right. \text{ or } C_6H_4\left\{\begin{matrix}C=NOOH\\ \quad>CH\\N\end{matrix}\right.$$

Permanganate oxidizes the nitroso-bodies into nitro-bodies. *β*-**Nitroso-indole** (?) decomposes at 170° (C. 1907, I. 1543).

β-**Nitroso-methylindole,** m.p. 198° with dec. **Nitroso-*α*-phenylindole,** m.p. 250°. *β*-**Nitro-indole,** yellow needles, m.p. 210°, is formed from *β*-nitro-indole-*α*-carboxylic acid, which proves its constitution. On further nitration with nitric acid in glacial acetic acid it yields *αβ*-**dinitro-indole,** decomposing at 260°. *β*-**Nitro-methylindole,** yellow scales, m.p. 248°, *β*-**nitro-*α*-phenylindole,** m.p. 239°–241°. Permanganate oxidizes this nitromethylindole to *β*-**nitro-indole-*α*-carboxylic acid** (C. 1903, II. 121; 1904, I. 1216; II. 710).

The *α*-substituted indoles also react excellently with the diazobenzene salts: *β*-**benzeneazomethylindole,** $(C_9H_8N)N:NC_6H_5$, m.p. 115°; *β*-**benzeneazo-*α*-phenylindole,** m.p. 166° (C. 1903, I. 839).

5. *Amino-indoles.*—**α-Amino-indole,** $C_8H_6N(NH_2)$, brilliant prisms (di-aceto-compound, m.p. 142°), is formed by the transposition of *o*-aminobenzyl cyanide on heating with alcoholic sodium ethylate: NH_2 (B. **43,** 2543), **β-Amino-methylindole,** $C_8H_5N(CH_3)(NH_2)$, m.p. 113°, and **β-Amino-α-phenylindole,** m.p. 180°, from the corresponding nitroso-compounds (see above) by reduction; with nitrous acid the β-amino-indoles yield yellow diazo-compounds of remarkable stability, probably derivable from the desmotropic formula of indole,  $\begin{matrix}N\\ \ddot{N}\end{matrix}\!\!>\!C\!<\!\!\begin{matrix}C_6H_4\\ C(R)\end{matrix}\!\!>\!N$ (*cf.* Quinondiazine, Vol. II., and C. 1905, II. 99; 1906,8 II. 1127). α-Amino-indole and *N*-ethyl-β-aminophenylindole, accordingly, form no diazo-compounds with HNO_2.

6. *Indolealdehydes* have been obtained by the action of chloroform and Na ethylate upon indoles, besides β-chloro-quinolines (see phenol aldehyde synthesis). **β-Indolealdehyde,** $C_8H_6N.CHO$, m.p. 195°, is also formed by the oxidation of tryptophane with $FeCl_3$ (see below). *Oxime,* m.p. 200°. $KMnO_4$ oxidizes it to β-indolecarboxylic acid. On heating with dilute mineral acids it forms a red dye (B. **39,** 2516; C. 1911, I. 1420).

α-Methyl-β-indolealdehyde, $C_8H_5N(CH_3).CHO$, m.p. 198°, has also been obtained by the action of amyl formate and sodium ethylate upon α-methylindole (C. 1907, I. 1135; 1908, I. 739).

7. *Indoleketones* are formed by the reaction of indyl magnesium iodide with acid chlorides (C. 1911, I. 1853). **β-Indyl methyl ketone,** $C_8H_6N.COCH_3$, m.p. 189°, and **β-indyl ethyl ketone,** $C_8H_6N.COC_2H_5$, m.p. 158°, yield β-indolecarboxylic acid on melting with caustic potash. **β-Indyl phenyl ketone,** $C_8H_6N.COC_6H_5$, m.p. 170°.

8. *Indole Carboxylic Acids.*—These are produced by the following synthetic methods: (1) from the phenylhydrazones of the pyroracemic acids, by reactions perfectly similar to those employed for the pyrrolecarboxylic acids; (2) when the indoles are heated with sodium and carbon dioxide; (3) by fusing the alkylindoles with caustic alkali. Ordinary oxidizing agents do not attack them (B. **21,** 1925). Heated alone, or with lime, they break down into carbon dioxide and indoles.

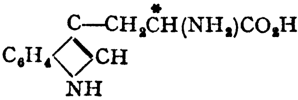
α-Indolecarboxylic acid, $C_8H_6N.CO_2H$, melting at 200° with decomposition, has been prepared from pyroracemic phenylhydrazone, from α-methylindole by the potash fusion, and by the latter process from *tetrahydrocarbazole.*

The acid also results in the reduction of *o*-nitrophenyl pyroracemic acid with zinc dust and glacial acetic acid, whereas the product will be *N*-hydroxyindolecarboxylic acid when sodium amalgam is used (see B. **30,** 1045). It yields an *imide* anhydride (B. **22,** 2503) corresponding to *pyrocoll* if heated with acetic anhydride.

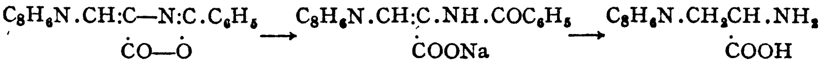
For derivatives of the acid, such as the hydrazide, azide, etc., see C. 1902, I. 1230.

β-Indolecarboxylic acid, $C_8H_6N.CO_2H$, m.p. 218° with dec., from skatole by potash fusion and from indole with CO_2 and Na (B. **43,** 3526), forms no imide anhydride (B. **23,** 2296). Its *nitrile,* m.p. 178°, is formed by the action of formic acid ester and sodium upon *o*-amino-benzyl cyanide, and from β-indole aldoxime by means of acetic anhydride (B. **43,** 2548). *N*,*a*-**Dimethylindole-*β*-carboxylic acid,** $C_8H_4N(CH_3)_2COOH$, m.p. 200°, from aceto-acetic ester methylphenyl hydrazone, $C_6H_5N(CH_3).N:C(CH_3).CH_2.COOR$.

β-**Indylacetic acid,** *skatole-ω-carboxylic acid,* (C_8H_6N)-*β*-CH_2CO_2H, m.p. 165°, synthetically from the phenylhydrazone of *β*-formyl propionic ester (Vol. I.), $C_6H_5NHN:CHCH_2CH_2COOC_2H_5$, by method 3 (B. **37,** 1801), is found in the putrefaction products of albumen, besides indole, skatole, and **indyl-*β*-propionic acid,** *skatoleacetic acid,* (C_8H_6N)-*β*-CH_2CH_2COOH, m.p. 134°, obtained synthetically from the phenyl hydrazone of γ-aldehydo-butyric acid ester (B. **38,** 2884). Both acids are obtained in the disintegration of *l*-**Tryptophane,** *β-Indylalanine,*



, m.p. about 289°, a hydrolytic fission product of most proteïns. Iron chloride oxidizes it to *β*-indole aldehyde, which formed the basis for its synthetic preparation. On the analogy of hippuric acid, it combines with benzaldehyde, sodium acetate, and acetic anhydride to form *a-benzoylaminoindylacrylic acid lactone,* which, on splitting up with caustic potash and reduction with Na and alcohol, splits off the benzoyl group and yields racemic tryptophane (Ellinger, B. **40,** 3029; C. 1908, I. 2180).

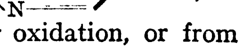


$$\underset{CO—O}{C_8H_6N.CH:C—N:C.C_6H_5} \longrightarrow \underset{COONa}{C_8H_6N.CH:C.NH.COC_6H_5} \longrightarrow \underset{COOH}{C_8H_6N.CH_2CH.NH_2}$$

Under the influence of the bacteria of putrefaction, tryptophane splits off CO_2 and passes into ω-**amino-*β*-ethylindole,** $C_8H_6N.CH_2.CH_2NH_2$, m.p. 146°, also obtained synthetically from the phenyl hydrazone of γ-aminobutyraldehyde by heating with $ZnCl_2$ (C. 1911, I. 1061). In the dog's body tryptophane is converted into *kynurenic acid,* or γ-hydroxyquinoline-*β*-carboxylic acid (*q.v.*).

On polypeptides of tryptophane, see B. **42,** 2331, 4320.

N-**Methylindyl-*β*-acetic acid,** m.p. 129°, from *N*-Methylindole with diazoacetic ester (C. 1899, I. 1073).

A *ββ*-**Diethylindolenine-*a*-carboxylic acid,** 

, is obtained from *ββ*-diethyl-*a*-methyl-indolenine by oxidation, or from the corresponding aldoxime, produced from *ββ*-diethyl-*a*-methyl-indolenine with N_2O_3 (C. 1899, I. 280; 1900, I. 867).

9. *Oxyindole Derivative.*—**Indoxyl, *β*-Hydroxyindole,** $C_6H_4<$

yellow crystals, m.p. 85°, is formed from indoxylic acid on heating with water, with rejection of CO_2 (B. **35,** 1701). By direct synthesis, indoxyl is obtained from methylanthranilic acid, and from phenyl-glycine, $C_6H_5NHCH_2COOH$, by fusing with sodium amide (compare indigo syntheses and C. 1903, I. 110, 111). The indigo-forming *indican* contained in the indigo plant is probably a glucoside of indoxyl (C. 1900, I. 1294; II. 874; 1910, I. 450). Indoxyl dissolves in water with a yellow fluorescence. It is rather unstable, and easily resinifies. In concentrated HCl it dissolves with a red colour. In alkaline solution it soon oxidizes in air to indigo blue; the oxidation is accelerated by ferric chloride:

$$\underset{\text{Indoxyl.}}{2C_8H_7ON}+2O=\underset{\text{Indigo Blue.}}{(C_8H_5ON)_2}+2H_2O.$$

On heating with potassium pyrosulphate, indoxyl forms the potassium salt of indoxylsulphuric acid, $C_8H_6N.O.SO_3K$, also found in the urine of plant-eating animals, and in human urine (urine indican) after the consumption of indole. On heating with acids the salt disintegrates with re-formation of indoxyl, which, on treating in the cold with a little $FeCl_3$, forms indigo blue (test for indoxylsulphuric acid in urine). Synthetically, the potassium salt of indoxylsulphuric acid has been obtained from phenylglycine-*o*-carboxylic acid by fusion with potash and subsequent treatment with potassium pyrosulphate.

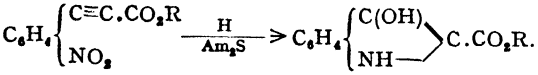
On shaking up the potash melt of phenylglycine-*o*-carboxylic acid with benzyl chloride, ***ON*-dibenzyl-indoxyl** is formed, m.p. 166° (C. 1897, I. 862). Acetic anhydride and free indoxyl yield ***N*-acetyl indoxyl,** $C_8H_6ON(COCH_3)$, m.p. 136°, and in alkaline solution ***O*-acetyl indoxyl,** $C_8H_6N(OCOCH_3)$, m.p. 126°. ***ON*-Diacet-indoxyl,** m.p. 82°, from *N*-acetylindoxyl, and also from anthranilino-acetic acid with acetic anhydride (B. **34,** 1854; C. 1902, II. 491).

For the action of halogens upon indoxyl, see C. 1902, I. 1344.

Indoxylaldehyde, $C_6H_4{<}\genfrac{}{}{0pt}{}{C(OH)}{N}{>}C.CHO$, brilliant needles decomposing at 160°, is formed on fusing indigo blue with caustic alkalies, besides anthranilic acid, with which it combines in the presence of acids with elimination of water to form the so-called *chrysanilic acid,* $C_8H_5ON.CH:NC_6H_4.COOH$ (B. **43,** 1971).

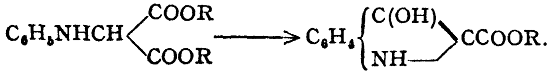
Indoxylic acid, $C_6H_4{<}\genfrac{}{}{0pt}{}{C(OH)}{NH}{>}C.COOH$, m.p. 123° with dec., is formed by fusion of its ethyl ester with caustic soda. The ester is prepared:

1. By $(NH_4)_2S$ reduction of *o*-nitrophenylpropiolic ester or its transposition product isatogenic acid ester. An intermediate member of this series is indoxanthenic acid ester (B. **15,** 745), obtained by oxidizing indoxylic acid ester:



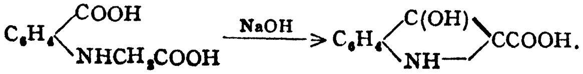
$$C_6H_4\left\{\begin{array}{l}C{\equiv}C.CO_2R\\NO_2\end{array}\right.\xrightarrow[Am_2S]{H}C_6H_4\left\{\begin{array}{l}C(OH)\\NH\end{array}\right.{>}C.CO_2R.$$

2. By condensation of anilino-malonic ester on heating to 260°–265° (B. **31,** 1816).



$$C_6H_5NHCH{<}\genfrac{}{}{0pt}{}{COOR}{COOR}\longrightarrow C_6H_4\left\{\begin{array}{l}C(OH)\\NH\end{array}\right.{>}CCOOR.$$

3. Industrial importance attaches to the formation of indoxylic acid from phenyl-glycine-*o*-carboxylic acid by heating with caustic alkalies:



$$C_6H_4{<}\genfrac{}{}{0pt}{}{COOH}{NHCH_2COOH}\xrightarrow{NaOH}C_6H_4{<}\genfrac{}{}{0pt}{}{C(OH)}{NH}{>}CCOOH.$$

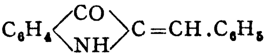
The esters of phenylglycine-*o*-carboxylic acid are condensed to indoxylic acid esters by merely treating with Na ethylate solution. The *N*-acidyl and *N*-alkyl derivatives act even more easily. From the latter we obtain *N*-alkyl indoxylic acid ester (B. **35,** 1683, 1699).

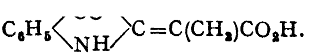
On heating with conc. H_2SO_4, indoxylic acid ester gives indigosulphonic acid quantitatively; this is converted into indigo by heating with alkali and blowing air through. On heating indoxylic acid ester to 240°–260° it is, like indole-*α*-carboxylic acid, converted into a bimolecular imide anhydride (B. **35,** 524).

It possesses a phenol character, which is indicated by its solution in alkalies, from which it is again precipitated by carbon dioxide. Ethyl iodide converts the salts of indoxylic ester into ethyl indoxylic ester, $C_8H_5(OC_2H_5)N.CO_2R$, which by saponification with baryta-water forms **ethyl-indoxylic acid.** This acid loses CO_2 when it is heated, and becomes ***O*-ethylindoxyl,** $C_8H_6(OC_2H_5)N$, which resembles indole in its chemical behaviour and in its odour. When digested with hydrochloric acid, ethylindoxylic acid yields *indoxyl,* and by nitrous acid is converted into *pseudoisatoxime.*

In many reactions indoxyl, as well as indoxylic acid, yields products which are derived from ***pseudo*indoxyl,** or *β-ketodihydroindole,* an isomeride of indoxyl, so that it may be assumed that in these instances $C_6H_4\left\langle\begin{matrix}C.OH\\NH\end{matrix}\right\rangle CH$ changes to $C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle CH_2$ (compare dihydroresorcinol, phloroglucinol, etc.).

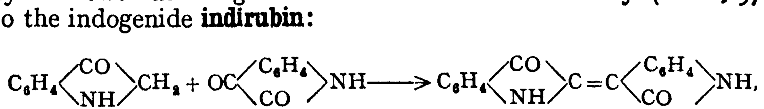
In the second form indoxyl and indoxylic acid react with aldehydes, ketones, and ketonic acids—*e.g.*, benzaldehyde, pyroracemic acid, etc. —with the production of so-called **indogenides.** The bivalent group, $C_6H_4<\begin{matrix}CO\\NH\end{matrix}>C=$, is termed *indogen* (B. **16,** 2197):


$$C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C=CH.C_6H_5$$
Indogenide of Benzaldehyde.

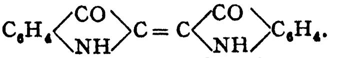

$$C_6H_5\left\langle\begin{matrix}--\\NH\end{matrix}\right\rangle C=C(CH_3)CO_2H.$$
Indogenide of Pyroracemic Acid.

The indogenides of protocatechualdehyde and of the aminobenzaldehydes have the character of dyestuffs (C. 1903, I. 34).

Isatin and benzene hydrocarbons also yield indogenides. Isatin may be viewed as *indogen oxide.* Isatin converts indoxyl (B. **17,** 976) into the indogenide **indirubin:**


$$C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle CH_2+OC\left\langle\begin{matrix}C_6H_4\\CO\end{matrix}\right\rangle NH\longrightarrow C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C=C\left\langle\begin{matrix}C_6H_4\\CO\end{matrix}\right\rangle NH,$$
ψ-Indoxyl. Isatin. Indirubin.

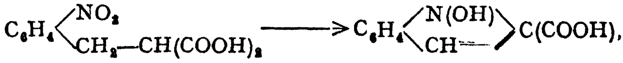
which is isomeric with indigo blue. The latter is also produced by the oxidation of indoxyl (p. 55); hence it may be viewed as **diindogen:**


$$C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C=C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4.$$
Indigo Blue (Diindogen).

Similarly, from indoxyl and thionaphthenquinone we obtain **β-thionaphthen-α-indole indigo,** $C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C=C\left\langle\begin{matrix}C_6H_4\\CO\end{matrix}\right\rangle S$ (M. **29,** 375), and from indoxyl and acenaphthenequinone the violet **acenaphthene-α-indole indigo,** $C_6H_4<\genfrac{}{}{0pt}{}{CO}{NH}>C:C<\genfrac{}{}{0pt}{}{CO}{C_{10}H_6}$ (B. **41,** 3332).

β-Ethoxy-α-methylindole, $C_8H_5N(O.C_2H_5)(CH_3)$, melting at 142°, is obtained from ethoxyacetone phenylhydrazone, $C_6H_5NHN:C(CH_3)CH_2\text{-}OC_2H_5$ (B. **25,** R. 417).

N-**Hydroxyindole-α-carboxylic acid,** melting at 159° with decomposition, is isomeric with indoxylic acid. It results on boiling *o*-nitrobenzylmalonic acid with sodium hydroxide:



$$C_6H_4\left\langle\genfrac{}{}{0pt}{}{NO_2}{CH_2\text{—}CH(COOH)_2}\right.\longrightarrow C_6H_4\left\langle\genfrac{}{}{0pt}{}{N(OH)}{CH\text{——}}\right\rangle C(COOH),$$

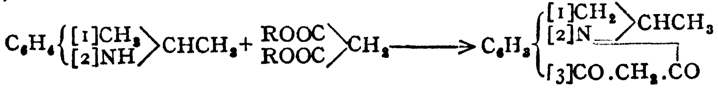
as well as by the reduction of *o*-nitrophenylpyroracemic acid with sodium amalgam. It is readily reduced to α-indole carboxylic acid. Potassium permanganate oxidizes it, with the possible intermediate production of phenylhydroxylamine-*o*-carboxylic acid, to *o*-azoxybenzoic acid, while with chromic acid it yields isatin. It can be very easily acidylated or alkylated in the NOH-group.

N-**Methoxyindole-α-carboxylic acid,** melting at 185° with decomposition, is also reduced to indolecarboxylic acid, and oxidized by chromic acid to *N*-**methoxy-ψ-isatin,** $C_6H_4\left\langle\genfrac{}{}{0pt}{}{CO\text{——}}{N(OCH_3)}\right\rangle CO$, consisting of red needles, melting at 110°. Bleaching powder, hydrogen peroxide, etc., convert *N*-hydroxyindolecarboxylic acid into **indoxin.** This is a blue-coloured, unstable dye, very similar to indigo, but soluble in alkalies. When it is dissolved in concentrated sulphuric acid and the diluted solution is allowed to stand exposed to the air, **indigo** separates. The yield is good (B. **29,** 639; **30,** 1045, 1052).

α-Phenyl-hydroxyindole, $C_8H_5N(C_6H_5)(OH)$, melting at 175°, is formed in the action of concentrated sulphuric acid upon benzoin oxime.

Hydro-indole Derivatives.—Indole may, though with some difficulty, be reduced electrolytically to **dihydro-indole,** *indoline,* $C_6H_4<\genfrac{}{}{0pt}{}{CH_2}{NH}>CH_2$, b.p. 221°, which can also be obtained from *N*-methylindoline by heating with HI and phosphorus (C. 1905, II. 335; 1908, II. 1263). *N*-**Benzoyl indoline,** m.p. 119°; **nitroso-indoline,** m.p. 84°. The reduction of the alkylated indoles is more easily effected electrolytically or with Sn and HCl. The hydro-indoles or indolines show a behaviour differing considerably from the mother substance. They closely approach the *alkylated anilines,* and are related to the tetrahydro-quinolines (*q.v.*) containing a six-membered hydrogenated pyridine ring condensed with the benzene nucleus (cyclic homology; compare B. **26,** 1285). By means of silver sulphate the dihydro-indoles can be oxidized back to indoles (B. **27,** 827). *N*-**Methylindoline,** $C_8H_8N(CH_3)$, b.p. 216° (A. **239,** 246).

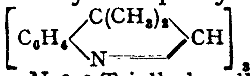
Dihydromethylindole, **α-methyl-indoline,** $C_9H_{11}N$, b.p. 227°, has been split up into optically active components by means of bromocamphorsulphonic acid (C. 1904, II. 1657). On heating with HI and phosphorus it yields *o*-propyl-aniline (C. 1898, II. 714). With malonic acid ester it yields a tricyclic condensation product (B. **26,** 1298):



$$C_6H_4\left\{\begin{matrix}[1]CH_2\\ [2]NH\end{matrix}\right\rangle CHCH_3 + \begin{matrix}ROOC\\ ROOC\end{matrix}\rangle CH_2 \longrightarrow C_6H_3\left\{\begin{matrix}[1]CH_2\rangle CHCH_3\\ [2]N\\ [3]CO.CH_2.CO\end{matrix}\right.$$

α,β-**Dimethylindoline,** $C_{10}H_{13}N$, b.p. 229°. *N*-**Methyldihydro-*β*-naphtho-pyrrole,** $C_{12}H_{10}N(CH_3)$, m.p. 41° (see B. **39,** 3140).

α,α-**Dimethylindoline,** $C_6H_4<\substack{CH_2\\NH}>C(CH_3)_2$, b.p. 210°, is formed on distilling *o-iso*propylaminobenzyl alcohol. The isomeric *ββ*-**dimethylindoline,** m.p. 35°, b.p. 228°, is obtained by the reduction of *ββ*-dimethylindolinone, or, better, from the condensation product of *iso*butylidene phenylhydrazone, the trimolecular *ββ*-**dimethylindolenine,**



by reduction (M. **18,** 115).

N, β, β-Trialkyl-*α*-alkylideneindolines such as **Trimethylmethyleneindoline,** $C_6H_4\left\{\substack{C(CH_3)_2\\N(CH_3)}\right\rangle C:CH_2$. b.p.$_{21}$ 129°; *N*-**Phenyl-*β, β*-dimethyl-*α*-methyleneindoline,** b.p.$_{52}$ 208°, and others, have been obtained synthetically from the unsymmetrical alkyl-phenyl-hydrazones of suitable ketones, and by the thorough alkylation of indoline; *N, ββ*-**trimethyl-*α*-benzylidene indoline,** m.p. 93°, from *Nββ*-trimethylindolinone and benzyl magnesium chloride (B. **38,** 1359). On oxidation they yield indolinones (see below).

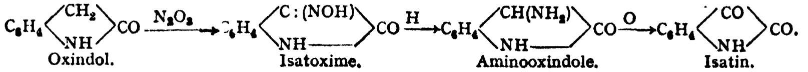
Oxygenated Derivatives of the Dihydro-indoles.—Indolinols and indolinones are also obtained synthetically from phenylhydrazine derivatives (S. 743): *N,β,β*-**Trimethylindolinole,** $C_6H_4<\substack{C(CH_3)_2\\N(CH_3)}>C<\substack{H\\OH}$, m.p. 95°, and *N*-**Phenyl-*β,β*-dimethylindolinole,** m.p. 125°, are obtained from the *unsym.* phenylmethyl- and the diphenyl-hydrazone of *iso*butyraldehyde with alc. HI or $SnCl_2$ or HCl. On heating with HCl, one methyl group migrates, and they are converted into trimethyl- and phenyldimethylindole respectively (M. **21,** 156).

Nββ-**Trimethyl-*α*-phenylindolinole,** m.p. 120°, from *Nββ*-trimethyl indolinone with C_6H_5MgBr (M. **27,** 1223).

α-Indolinones can also be regarded as lactams of the *o*-aminophenylacetic acid series, and have been to some extent already described as such. In this connection, special interest attaches to the synthesis from *acidyl phenylhydrazides* on heating with lime (M. **18,** 95, 527; *cf.* C. 1910, I. 876): $C_6H_5NH.NH.COCH_3 \longrightarrow C_6H_4\left\{\substack{CH_2\\NH}\right\rangle CO$; Similar reactions are shown by the propionyl, butyryl, *iso*butyryl, and phenacetyl phenylhydrazides, and by the propionyl- and *iso*butyryl methylphenylhydrazides: *β*-**methyl-*α*-indolinone,** m.p. 123°. *β-Ethyl-* and *β-phenyl-indolinone,* m.p. 102° and 183°; *β-iso***propyl-indolinone,** m.p. 106° (C. 1903, II. 887). *ββ*-**Dimethyl indolinone,** m.p. 151°. *Nββ*-**Trimethyl indolinone,** m.p. 47°, b.p. 265°, is formed from the corresponding indolinol, and from the trimethyl alkylidene indolines by oxidation.

Among the oxygenated hydroindole derivatives we may specially mention the following substances, forming a transition to indigo blue or indigotin:

1. **Oxindole,** *a-indolinone,* $C_6H_4<\begin{matrix}CH_2\\NH\end{matrix}>CO$, obtained from acetophenylhydrazide with lime. It was first obtained by the reduction of dioxindole, and easily reverts to the latter in air. It therefore reduces ammoniacal silver solution. With N_2O_3 it forms isatoxime, which on reduction becomes *amino-oxindole* and by subsequent oxidation isatin:



$$C_6H_4<\begin{matrix}CH_2\\NH\end{matrix}>CO \xrightarrow{N_2O_3} C_6H_4<\begin{matrix}C:(NOH)\\NH\end{matrix}>CO \xrightarrow{H} C_6H_4<\begin{matrix}CH(NH_2)\\NH\end{matrix}>CO \xrightarrow{O} C_6H_4<\begin{matrix}CO\\NH\end{matrix}>CO.$$

Oxindol. Isatoxime. Aminooxindole. Isatin.

Oxindole combines with aldehydes and ketones with elimination of water to form coloured compounds showing geometrical isomerism with the indogenides from indoxyl. These are called *iso-indogenides.*

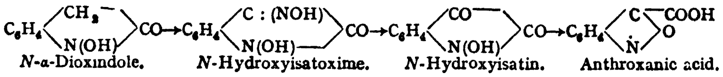
Benzal-oxindole, $NH<\begin{matrix}C_6H_4\\CO\end{matrix}>C:CHC_6H_5$, sulphur-yellow needles melting at 176°. From oxindole and isatin we obtain a substance isomeric with indigo blue and indirubin.

Isoindigotin, $NH<\begin{matrix}C_6H_4\\CO\end{matrix}>C:C<\begin{matrix}C_6H_4\\CO\end{matrix}>NH$ (C. 1909, I. 1575; II. 832).

Oxindolealdehyde, $C_6H_4<\begin{matrix}C(CHO)\\NH\end{matrix}>COH$, yellow needles, m.p. 213°, is formed, besides thio-salicylic acid, in the fission of thio-indigo scarlet with alkali (B. **43,** 1974).

2. **Dioxindole,** $C_6H_4<\begin{matrix}CH.OH\\NH\end{matrix}>CO$, is obtained from nitromandelic acid and from isatin by reduction with zinc dust and acetic acid (B. **37,** 938). Oxidation converts it back into isatin and isathide (see below). β-Alkyl- and aryl-dioxindoles, $C_6H_4<\begin{matrix}C(OH)R\\NH\end{matrix}>CO$, have been obtained by transforming isatin by means of organo-magnesium compounds (C. 1910, II. 1140).

3. *N*,*a*-**Dioxindole,** $C_6H_4<\begin{matrix}CH_2\\N(OH)\end{matrix}>CO$, colourless rhombic plates, aceto-compound, m.p. 101°, is obtained by reducing *o*-nitrophenyl acetic acid with zinc dust and sulphuric acid. With HNO_2 it yields *N*-**hydroxyisatoxime,** m.p. 223°, from which by successive reduction and oxidation *N*-**hydroxyisatin** is obtained. This easily transposes into the isomeric anthroxanic acid under the influence of acids and alkalies (B. **41,** 3921):



$$C_6H_4<\begin{matrix}CH_2\\N(OH)\end{matrix}>CO \rightarrow C_6H_4<\begin{matrix}C:(NOH)\\N(OH)\end{matrix}>CO \rightarrow C_6H_4<\begin{matrix}CO\\N(OH)\end{matrix}>CO \rightarrow C_6H_4<\begin{matrix}C-COOH\\N\end{matrix}>O$$

N-a-Dioxindole. *N*-Hydroxyisatoxime. *N*-Hydroxyisatin. Anthroxanic acid.

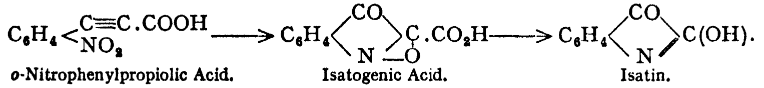
4. *N*,*a*,β-**Trioxindole,** $C_6H_4<\begin{matrix}CH(OH)\\N(OH)\end{matrix}>CO$, m.p. 172° with dec., the anhydride of *o*-hydroxylamino-mandelic acid, is formed by the reduction of *o*-nitromandelic acid with zinc dust and ammonia. On heating by itself or warming with acetic anhydride it splits off water and passes into isatin, while, on careful oxidation with $KMnO_4$, it passes into *N*-hydroxyisatin (B. **42,** 470).

Isatin, $C_6H_4<\begin{matrix}CO\\NH\end{matrix}>CO$, or $C_6H_4<\begin{matrix}CO\\N\end{matrix}>C.OH$. Its properties are given in Vol. II., p. 389. The following methods for its formation may be especially mentioned:

1. The oxidation of indigo with nitric acid (*Method of preparation,* J. pr. Ch. [2], **24,** 11; **25,** 434).

2. The oxidation of *oxindole* and *dioxindole.*

3. The action of alkali upon o-*nitrophenylpropiolic acid,* when there occurs at first a rearrangement into *isatogenic acid,* which then loses carbon dioxide and becomes isatin:



o-Nitrophenylpropiolic Acid. Isatogenic Acid. Isatin.

If a reducing agent be added to the alkaline solution of the *o*-nitrophenylpropiolic acid, *indigo* will result instead of isatin (see below).

4. From the easily synthesized isatin-*α*-anil, $C_6H_4<{CO \atop NH}>C:NC_6H_5$, isatin is obtained by heating with dilute mineral acids (C. 1900, II. 929).

5. Oxanilide chloride, $C_6H_5N : ClCl.CCl : NC_6H_5$, on warming with conc. H_2SO_4, passes into isatin (C. 1908, I. 1001).

Technical importance attaches only to the processes with trioxindole and isatin-*α*-anil.

Behaviour.—(1) *Isatoic Acid,* $C_6H_4\left\langle{N.COOH \atop CO}\right.$, is formed when isatin is oxidized with chromic acid in glacial acetic acid solution.

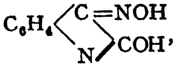
Isatin yields *nitrosalicylic acid* when oxidized with nitric acid.

(2) When reduced with ammonium sulphide we get first isatide, $C_{16}H_{12}N_2O_4$, then dioxindole and oxindole.

(3) Ammonia and primary amines form **Imesatins** of the general formula $C_6H_4\left\langle{C=NR \atop NH>CO}\right.$, which, when digested with alkalies, decompose again into isatin and amines.

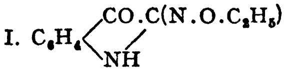
o-Phenylenediamine yields *indophenazine* (B. **29,** 194, 1030); piperidine yields a *dipiperidyl isatin,* $C_8H_5NO(NC_5H_{10})_2$, which can be converted into a dye—*isatin blue*—similar to indigo (B. **24,** 1366). (4) Isatin condenses, further, with benzene hydrocarbons, phenols, etc., with loss of water. It forms with thiophen the blue dye *indophenin,* ($C_8H_5NO_2 + C_4H_4S - H_2O$). Similar products are obtained with furan and pyrrole (B. **40,** 2492). (5) The dark violet alkali salts of isatin are derivable from its lactam formula, since benzoyl chloride converts them into ***N*-benzoyl-*ψ*-isatin,** m.p. 206°, and methyl and ethyl iodides give ***N*-methyl-*ψ*-isatin** and ***N*-ethyl-*ψ*-isatin** respectively, m.p. 134° and 95°, also formed from *N*-methyl- and *N*-ethyl-indole by means of NaOBr (B. **40,** 1291). ***N*-Acetyl-*ψ*-isatin,** $C_6H_4(C_2O_2)N.CO.CH_3$, from isatin and acetic anhydride. (6) The hydroxyl or lactim formula of isatin furnishes alkali salts; from the solution of the latter silver nitrate precipitates **silver isatin,** $C_8H_4(OAg)NO$, with which alkyl iodides yield O-alkyl isatins: **methylisatin,** $C_8H_4(OCH_3)NO$, melting at 102°; **ethylisatin,** $C_8H_4(OC_2H_5)NO$, melting at 88°, which can be resaponified to isatin or isatinates. (7) Similarly, *two isomeric* iso*nitroso-compounds* are derived from isatin: isatoxime and *pseudo*-isatoxime.

Isatoxime,



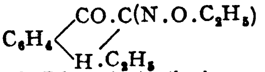
$C_6H_4\left\langle {C=NOH \atop N} \right\rangle COH$, melts at 202° with decomposition. It is prepared from isatin and hydroxylamine; or from oxindole by action of nitrous acid, and when reduced it yields so-called amino-oxindol, which can be oxidized to isatin. By the successive action of ethyl iodide upon the silver salt we obtain a *mono-* and a *diethyl* derivative from which isatin (B. **16,** 1706) is formed after saponification, which would indicate that the ethyl groups are combined with oxygen.

pseudo-**Isatoxime,** $C_6H_4<{CO \atop NH}>C=N.OH$, melting with decomposition at 200°, is prepared by the action of nitrous acid upon ethyl indoxylic acid. Ethyl iodide converts it into (1) a *mono-* and (2) a *diethyl* derivative. The first alone yields isatin, whereas the second is converted into *N*-methyl-ψ-isatin:

I. 

$C_6H_4\left\langle {CO.C(N.O.C_2H_5) \atop NH} \right.$

*Pseudo*isatin-ethoxime.

and II. 

$C_6H_4\left\langle {CO.C(N.O.C_2H_5) \atop N.C_2H_5} \right.$

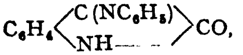
N,-Ethyl-ψ-isatin-ethoxime.

The reduction of *N*-ethyl-ψ-isatin-ethoxime produces *N-diethyl indigo* (B. **16,** 2201).

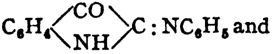
A dioxime is formed by *N*-acetyl-ψ-isatin and hydroxylamine. See B. **29,** 1030, for **isatin semicarbazone,** $C_8H_5NO(:NNHCONH_2)$.

Isatin-β-phenylhydrazone, $C_8H_5NO(:N.NHC_6H_5)$, m.p. 211°, from isatin and phenylhydrazine; the isomeric *pseudo*-**isatin phenyl hydrazone, isatin-α-phenylhydrazone,** m.p. 236°, has been obtained by transposition of *o*-methylisatin with phenylhydrazine or by the action of diazobenzene chloride upon indoxyl (B. **40,** 1298).

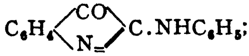
(8) In a similar manner, two position-isomeric isatin anils are derived from isatin: **Isatin-β-anil,**



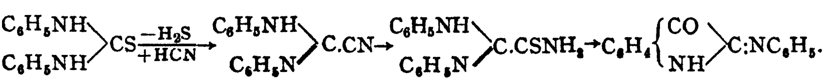
$C_6H_4\left\langle {C(NC_6H_5) \atop NH} \right\rangle CO$, golden-yellow prisms, m.p. 221°, and **isatin-α-anil,** occurring in two modifications, yellowish-brown flakes and violet prisms respectively, m.p. 216°, probably corresponding to the lactam and lactim forms of isatin according to the formulæ:



$C_6H_4\left\langle {CO \atop NH} \right\rangle C:NC_6H_5$ and



$C_6H_4\left\langle {CO \atop N} \right\rangle C.NHC_6H_5$; on heating, the former passes into the latter. Isatin-α-anil is obtained from isatin chloride or O-methylisatin with aniline, or from indoxyl or indoxylic acid with nitrosobenzene (B. **42,** 4269). Industrially, a start is made with diphenyl thiourea, which, on eliminating sulphur by means of lead carbonate, gives *carbo-diphenylimide.* This passes into its hydro-cyanide on treating with alkaline cyanide and HCN. The hydro-cyanide, treated with yellow Am_2S, yields a thiamide, which on heating with conc. H_2SO_4, condenses to **isatin-α-anil** (C. 1900, II. 928, 929, 1250; 1901, I. 71; D.R.P. 113979):



$$\begin{matrix}C_6H_5NH\\C_6H_5NH\end{matrix}\Big\rangle CS \xrightarrow[+HCN]{-H_2S} \begin{matrix}C_6H_5NH\\C_6H_5N\end{matrix}\Big\rangle C.CN \rightarrow \begin{matrix}C_6H_5NH\\C_6H_5N\end{matrix}\Big\rangle C.CSNH_2 \rightarrow C_6H_4\begin{cases}CO\\NH\end{cases}\Big\rangle C:NC_6H_5.$$

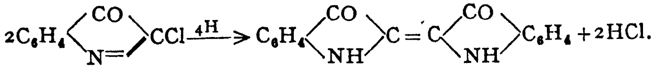
Finally, isatin-α-anil is also obtained by condensation of the body resulting from the action of aniline and hydroxylamine upon chloral.

***iso*Nitroso-ethenyldiphenylamidine,** $\substack{C_6H_5NH\\C_6H_5\ N}>C.CH{:}NOH$, with conc. H_2SO_4 (C. 1900, II. 929).

With H_2S in acid solution, isatin-α-anil yields **α-thio-isatin,** $C_6H_4(C_2OSNH)$, which easily gives up sulphur and yields indigo, and in alkaline lead solution gives isatin (C. 1902, I. 1429).

Am_2S reduces isatin anil in the cold to indoxyl, and on heating to indigo (B. **43,** 1379). Reduced with sodium hydrosulphite, the isatin aniles take up two H-atoms and pass into the colourless **isatin-leucanils,** $C_8H_7NO.NHC_6H_5$, which re-oxidize to isatin anils in air (B. **43,** 1376). **Isatindianil,** $C_6H_4(C:NC_6H_5)_2NH$, m.p. 210°.

(9) On heating isatin with PCl_5 in benzene solution we obtain **isatin chloride,** $C_6H_4<\substack{CO\\N}>CCl$, m.p. 180° with dec., which dissolves in ether with a blue colour. Reduction with HI in glacial acetic acid or zinc dust converts it into *indigo blue:*

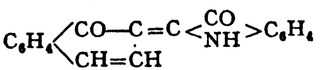


$$2C_6H_4<\substack{CO\\N=}>CCl \xrightarrow{4H} C_6H_4<\substack{CO\\NH}>C=C<\substack{CO\\NH}>C_6H_4+2HCl.$$

Similarly, the isatins substituted in the benzene nucleus give rise to substitution products of indigo blue: *Dibromo-, dinitro-, dimethyl indigo blue.*

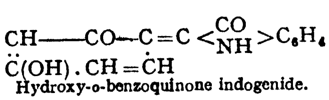
(10) With substances containing a reactive methylene group, isatin condenses with elimination of water to form *indigoid dyes,* resembling indigo in structure and behaviour. Thus, isatin and indoxyl give *Indirubin,* $C_6H_4<\substack{CO\\NH}>C:C<\substack{C_6H_4\\CO}>NH$, and isatin and β-hydroxy-thionaphthene give the industrially important *Thioindigo-scarlet-R,* $C_6H_4<\substack{CO\\S}>C:C<\substack{C_6H_4\\CO}>NH$ (M. **29,** 376); while in the case of isatin itself it is always the carbonyl in the β-position which reacts; α-isatin derivatives like isatin chloride, isatin-α-anil, and O-methyl isatin split off HCl, $C_6H_5NH_2$, and CH_3OH, and yield the geometrically isomeric dyes. Thus, indoxyl gives indigo blue, and β-hydroxy-thionaphthen yields **α-thionaphthen-α-indole indigo,** *Ciba Violet,* $C_6H_4<\substack{CO\\S}>C:C<\substack{CO\\NH}>C_6H_4$ (M. **29,** 377; **31,** 55).

Reactions with isatin chloride and isatin anilide are also shown by phenols which tend to pass into the keto form, like α- and β-naphthol, anthranol, α- and β-anthrol, resorcinol, etc. They usually form blue to bluish-violet indigoid vat dyes. (P. Friedländer, M. **29,** 375, 387; **30,** 271, 871) *e.g.:*



$$C_6H_4\left\langle\begin{array}{l}CO-C=C<\substack{CO\\NH}>C_6H_4\\CH=CH\end{array}\right.$$

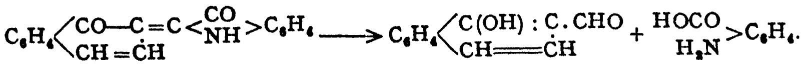
αβ-Naphthoquinone indogenide.



$$\begin{array}{l}CH—CO—C=C<\substack{CO\\NH}>C_6H_4\\C(OH).CH=CH\end{array}$$

Hydroxy-o-benzoquinone indogenide.

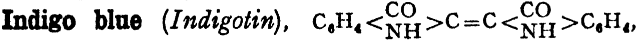
Alkalies break up these dyes more or less easily into anthranilic acid and the corresponding aldehydes:



$$C_6H_4\left\langle\begin{array}{l}CO-C=C<\substack{CO\\NH}>C_6H_4\\CH=CH\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}C(OH):C.CHO\\CH=CH\end{array}\right. + \substack{HOCO\\H_2N}>C_6H_4.$$

Compare the analogous breaking up of indigo blue (below).

α- and **β-Naphtisatin,** $C_{10}H_6(C_2O_2)NH$, m.p. 255° and 248° (see B. **21,** 117; **36,** 1736; C. 1904, II. 71).

Indigo blue (*Indigotin*),  $C_6H_4<\substack{CO\\NH}>C=C<\substack{CO\\NH}>C_6H_4$, constitutes the principal ingredient of commercial **Indigo,** derived from different *Indigoferæ,* from woad (*Isatis tinctoria*), and from the Sudan gara (*Lonchocarpus cyanescens*). It occurs in these plants as probably a glucose compound of indoxyl, $C_8H_6ON(C_6H_{11}O_5)$, called *indican,* which splits up into glucose and indoxyl when boiled with dilute acids, or if acted upon with a ferment. If the various portions of the plant be covered with water and exposed to the action of the air, the indoxyl is oxidized to indigo blue (C. 1898, II. 203; 1900, I. 1294; II. 874; 1909, II. 218; B. **35,** 4338). Much synthetic indigo is now made in Germany, and has largely displaced the plant indigo from Bengal, Java, and Central America.

Commercial indigo contains, in addition to 20–90 per cent. of indigo blue, various other substances, which have not been well studied, like *indigo gluten, indigo brown,* and *indigo red,* which are removed by successive treatment with dilute acetic acid, caustic potash, and hot alcohol.

A better procedure consists in first reducing indigo by means of grape-sugar and sodium hydroxide to soluble indigo white, which can then be oxidized to indigo blue by the exposure of the alkaline solution to the air, when the indigo blue will separate in a pure condition (A. **195,** 305).

History.—Indigo was in ancient times highly prized as a dye by the Oriental nations (Dioscorides, Pliny: ἴνδικον, indicum). In Europe it found general application in dyeing, from the opening up of sea-intercourse with the East Indies in the sixteenth century. To-day the production of indigo from plants, chiefly in Bengal, Java, Central America, is about 8,300,000 kg., equivalent in money to about $20,000,000.

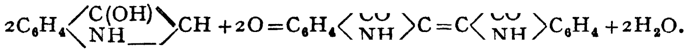
In the period of the alchemists indigo was quite frequently considered in Europe as a mineral or metal (compare Schultz: Steinkohlentheer, 2 Auflg., II. 883), presumably because of its copper-like lustre. More careful investigations into its chemical nature were first instituted in the last century. Erdmann and Laurent observed simultaneously (1841) that nitric acid oxidized indigo to isatin, while Fritzsche found (1848) that aniline resulted when it was distilled with caustic potash. Baeyer and Knop (1865) reduced it to dioxindole, oxindole, and indole. The latter body Baeyer and Emerling (1869) obtained synthetically from *o*-nitrocinnamic acid, and when Nencki (1874) succeeded in oxidizing indole to indigo with ozone, the first synthesis of this interesting compound was achieved (compare, however, Engler, B. **28,** 312). Baeyer and his students (1870-78) demonstrated the constitution and synthesis of oxindole or *o*-aminophenylacetic acid lactam, its conversion into isatin, as well as various methods for the conversion of isatin into indigo blue. Claisen and Shadwell (1879) also obtained isatin from *o*-aminobenzoylformic acid. Baeyer (1880-82), by a series of new syntheses of indigo, produced more certain evidence of its constitution and found easy methods for its production.

Out of the many indigo syntheses since devised, that of indigotin, discovered by Heumann in 1890 from phenylglycine or phenylglycine-*o*-carboxylic acid with alkali fusion followed by oxidation, has gradually attained an industrial importance (see C. 1901, I. 1325).

SYNTHESES OF INDIGO BLUE.

Most methods in the direct synthesis of indigo start from isatin or indoxyl and their derivatives; even plant indigo probably owes its formation to an oxidation of indoxyl.

(1) Indoxyl is oxidized to indigo:



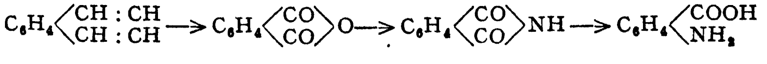
$$2C_6H_4\left\langle\begin{matrix}C(OH)\\NH\end{matrix}\right\rangle CH + 2O = C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{=}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4 + 2H_2O.$$

Indoxyl and its derivatives are prepared industrially in two ways:

(*a*) The first of these is based upon Heumann's discovery (1890) of the formation of indoxyl from *anilino-acetic acid* or *phenylglycine*, $C_6H_5NH.CH_2COOH$, by alkaline fusion. By an addition of sodium amide the fusion-point is lowered and made suitable for large-scale operations (C. 1903, I. 110).

Analogous to phenyl glycocoll are tolyl-, xylyl-, naphthyl-, and phenyl methyl-glycocoll, which form derivatives of indigo blue; with fuming sulphuric acid these bodies form the corresponding indigo sulphonic acids (B. **23**, 3043, 3431; **24**, R. 380; **25**, R. 488; **26**, 2547, R. 633). *Hydroxyethylaniline*, $C_6H_5NH.CH_2CH_2OH$ (C. 1906, II. 386), *Ethylendianiline*, $C_6H_5NHCH_2.CH_2NHC_6H_5$ (C. 1910, I. 1200), *Phenylhydantoïn* (C. 1902, II. 173), *Bromacetanilide*, $C_6H_5NHCO.CH_2Br$, and diphenyldiketo-piperazine, fused with potash, also yield indoxyl (B. **23**, 3289; C. 1900, II. 581; 1902, I. 476; 1904, I. 771). This group of syntheses also comprises the formation of indigo from ethyleneanthranilic acid, $C_6H_4<\genfrac{}{}{0pt}{}{NHCH_2CH_2NH}{COOH\quad HOOC}>C_6H_4$, by fusion with potash (B. **28**, 1685).

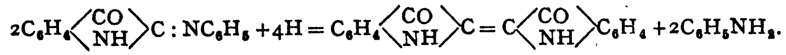
(*b*) Another method of preparing indoxyl and its derivatives starts from *anthranilic acid* (*q.v.*). The latter is derived from the naphthalene abundantly contained in coal-tar. On oxidation with H_2SO_4 and mercury, it gives phthalic acid anhydride, which is converted into phthalimide with NH_3, and then with bromine and alkali into anthranilic acid:



$$C_6H_4\left\langle\begin{matrix}CH:CH\\CH:CH\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle O \longrightarrow C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle NH \longrightarrow C_6H_4\left\langle\begin{matrix}COOH\\NH_2\end{matrix}\right.$$

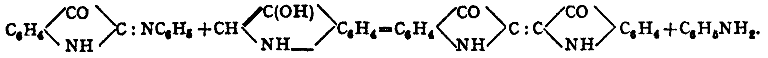
The anthranilic acid is (1) heated with chloracetic acid; or (2) condensed with formaldehyde and HCN and then saponified; or (3) fused with polyhydroxyl compounds like glycerine, mannitol, glucose, cellulose, etc., and caustic potash (B. **43**, 2774). The result of these processes is *anthranilino-acetic acid* or *phenylglycine-*o*-carboxylic acid*, $C_6H_4<\genfrac{}{}{0pt}{}{COOH}{NHCH_2COOH}$, which on further fusion with potash with exclusion of air or by heating with acetic anhydride passes into indoxyl derivatives, and further into indigo, as sketched above (see also the syntheses of indoxyl carboxylic ester and its conversion into indoxylic acid and indoxyl, above).

(2*a*) Isatin may be converted into isatin chloride and then with Zn dust into indigo, or isatin-*a*-anil is reduced to indigo with Am_2S (C. 1901, I. 867):



$$2C_6H_4\left\langle {CO \atop NH} \right\rangle C:NC_6H_5+4H=C_6H_4\left\langle {CO \atop NH} \right\rangle C=C\left\langle {CO \atop NH} \right\rangle C_6H_4+2C_6H_5NH_2.$$

(2*b*) Isatin chloride and isatin-*a*-anil condense to indigo when heated with indoxyl in benzene or glacial acetic acid, splitting off HCl and aniline respectively:

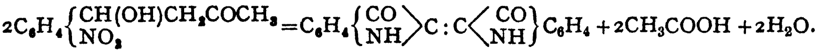


$$C_6H_4\left\langle {CO \atop NH} \right\rangle C:NC_6H_5+CH\left\langle {C(OH) \atop NH\_\_} \right\rangle C_6H_4=C_6H_4\left\langle {CO \atop NH} \right\rangle C:C\left\langle {CO \atop NH} \right\rangle C_6H_4+C_6H_5NH_2.$$

This method permits the preparation of unsymmetrically substituted indigotins.

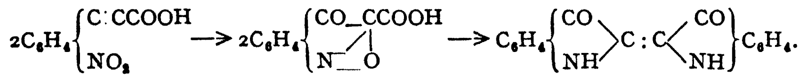
The following older syntheses (3), (4), and (5) of indigo, carried out by A. v. Baeyer and his assistants, have hardly more than a theoretical interest:

(3) *o*-Nitrobenzaldehyde condenses with acetone to form *β-hydroxy-o-nitrophenylethyl methyl ketone,* which is by alkalies clearly split up into acetic acid, water, and indigo blue:



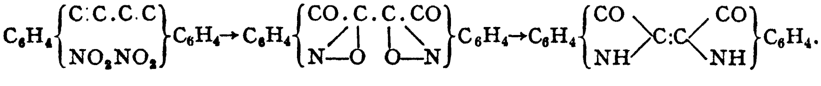
$$2C_6H_4\left\{ {CH(OH)CH_2COCH_3 \atop NO_2} \right. = C_6H_4\left\{ {CO \atop NH} \right\rangle C:C\left\langle {CO \atop NH} \right\} C_6H_4+2CH_3COOH+2H_2O.$$

(4) *o*-Nitrophenylpropiolic acid is transposed into isatogenic acid by alkaline reducing agents and, further, to indigo with loss of CO_2.



$$2C_6H_4\left\{ {C:CCOOH \atop NO_2} \right. \longrightarrow 2C_6H_4\left\{ {CO\_CCOOH \atop N\_O} \right. \longrightarrow C_6H_4\left\{ {CO \atop NH} \right\rangle C:C\left\langle {CO \atop NH} \right\} C_6H_4.$$

(5) *o*-Nitrophenylpropiolic acids can also be converted into *o*-nitrophenylacetylene by elimination of CO_2, whereupon its Cu compound is condensed by potassium ferricyanide to *dinitro-diphenyl diacetylene;* the latter is converted by alkali into di-isatogen, and by reduction into indigo:



$$C_6H_4\left\{ {C:C.C.C \atop NO_2NO_2} \right\} C_6H_4 \rightarrow C_6H_4\left\{ {CO.C.C.CO \atop N—O\ \ O—N} \right\} C_6H_4 \rightarrow C_6H_4\left\{ {CO \atop NH} \right\rangle C:C\left\langle {CO \atop NH} \right\} C_6H_4.$$

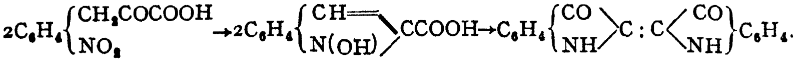
(6) On carefully heating *o-nitro-acetophenone,* $C_6H_4(NO_2)COCH_3$, with Zn dust a sublimate of indigo is formed in small quantities.

Benzylidene-o-nitroacetophenone, $C_6H_4<{COCH:CHC_6H_5 \atop NO_2}$ (2 mol.), splits up into indigo and benzoic acid under the influence of sunlight (B. **28**, 2497).

(7) o-*Nitrobenzoylacetic acid,* $C_6H_4<{CO.CH_2.COOH \atop NO_2}$, and its esters pass into indigo on heating with caustic alkalies and adding reducing agents (C. 1908, II. 920).

(8) N-*Hydroxyindolecarboxylic acid,* obtained from *o*-nitrobenzyl malonic ester or from *o*-nitrophenylpyroracemic acid, passes into

indigo on treating it with conc. sulphuric acid and oxidizing in air:



$$2C_6H_4\begin{cases}CH_2COCOOH\\NO_2\end{cases}\rightarrow 2C_6H_4\begin{cases}CH{=\!=}\\N(OH)\end{cases}\!\!>CCOOH\rightarrow C_6H_4\begin{cases}CO\\NH\end{cases}\!\!>C:C<\begin{matrix}CO\\NH\end{matrix}\Big\}C_6H_4.$$

Constitution of Indigo Blue.—The formula adopted for indigo is based upon the following facts:

1. The vapour density corresponds to the molecular formula $C_{16}H_{10}N_2O_2$.

2. The ready formation of indigo blue from indoxyl and isatin, as well as its easy conversion into these bodies and into other indole derivatives, is an argument in favour of the view that the indigo formula is produced by the union of two groups: $C_6H_4<{}^{\ddot{C}}_{N}>C$.

3. That these two residues must be linked to each other by C-union is evidenced by the synthesis from di-(*o*-nitrophenyl)-diacetylene (see above), which would indicate that diphenyldiacetylene, $C_6H_5C:C—C:C.C_6H_5$, is the parent hydrocarbon of indigo.

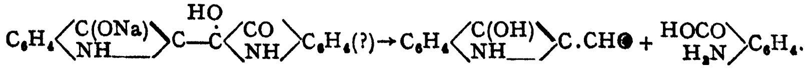
4. The formation of *N*-diethyl indigo from *N*-ethyl-*ψ*-isatin shows the presence of NH-groups.

Properties.—Indigo blue is a dark-blue powder with a reddish glimmer; it becomes metallic and copper-like under pressure. It sublimes in copper-red, metallic, shining prisms. It is insoluble in water, alcohol, and ether, in alkalies and dilute acids, and is odourless and tasteless. It dissolves in hot aniline with a blue, in molten paraffin with a purple-red, colour (this behaviour recalls the various colours of iodine solutions), and can be crystallized from these solvents in rhombic, strongly dichroic crystals (C. 1900, I. 771). It crystallizes from hot oil of turpentine in beautiful blue plates. Heated at the ordinary pressure, it partially decomposes and is converted into a dark-red vapour. The same occurs with decomposition under 30 to 40 mm. pressure. See B. **18**, 1426, for the absorption spectrum of indigo and its derivatives.

Woollen goods are dyed in two ways with indigo: (1) The wool is immersed in the aqueous solution of indigotin sulphonic acid, which fixes itself directly (Saxony blue dyeing); or (2) the indigo blue is changed by fermentation to indigo white (indigo vat), the cloth saturated with the latter and exposed to the air, when indigo blue forms and sets itself upon the fibre.

Indigo combines with both acids and alkalies. Thus, by dissolving indigo in glacial-acetic-sulphuric acid and adding ether, the crystalline sulphate, $C_{16}H_{10}N_2O_2.SO_4H_2$, is obtained (A. **325**, 196).

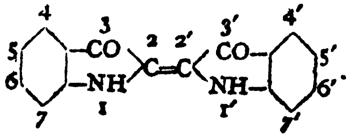
On treating indigo with conc. aqueous caustic soda or sodium alcoholate solution at ordinary temperature, we obtain an addition product, $C_{16}H_{10}N_2O_2.NaOH$, in the form of a dark-green powder dissociated by water, which, on strong action by alkali, splits up into *a*-indoxyl aldehyde and anthranilic acid (B. **43**, 1971):



$$C_6H_4<\begin{matrix}C(ONa)\\NH\text{\_\_\_}\end{matrix}>C—\overset{HO}{\dot{C}}<\begin{matrix}CO\\NH\end{matrix}>C_6H_4(?)\rightarrow C_6H_4<\begin{matrix}C(OH)\\NH\text{\_\_}\end{matrix}>C.CHO+\begin{matrix}HOCO\\H_2N\end{matrix}>C_6H_4.$$

Derivatives and Substitution Products of Indigo Blue.—Compare Ch. Ztg. **35,** 1158.

The substituents are usually indicated by the following scheme:



On treating with alkaline hydroxylamine solution indigo gives a monoxime, $C_{16}H_{10}N_2O(NOH)$, brownish-violet needles, m.p. 205° with dec. (B. **31,** 1252).

Symmetrical substitution products of indigo have been obtained from substituted phenylglycines (B. **41,** 3796), phenylglycine-*o*-carboxylic acids, isatins, *o*-nitroacetophenones, *o*-nitrophenyl lactic acid ketones, etc.; unsymmetrical ones by condensation of substituted isatin chlorides and *α*-isatin anils with indoxyl. Special technical interest attaches to the halogenated indigotins, out of which those substituted in the 5 and 7 positions are particularly distinguished by a greenish tint and great permanence. Substitution in the 6-position yields reddish-violet dyes: 5,7,5',7'**-tetra-chlorindigo,** *Brilliant Indigo,* and 5,7,5',7'**-tetra-bromindigo,** *Ciba Blue.*

They can be obtained by the direct halogenation of indigo in the absence of water, best in warm nitrobenzene solution (C. 1908, I. 1014); or in conc. H_2SO_4 or cold chloro-sulphonic acid; or by the action of halogen upon the sodium bisulphite compound of dehydro-indigo (B. **42,** 4408; **43,** 937). A special interest attaches to 6,6'**-dibromindigo,** dark violet crystals with a coppery lustre, which has been found to be identical with the purple of antiquity, gathered from the secretion of the Purple Snail, *Murex brandaris.* It colours the fibre a dark violet merging into red (Friedländer, B. **42,** 765). 7,7'**-Dimethyl indigo** (see B. **42,** 3641). *N*-**Dimethyl indigo,** $(C_6H_4{:}\,C_2ON.\text{-}C_2H_5)_2$, from ethyl-*ψ*-isatin ethyl oxime.

α- and *β*-**Naphthindigo** are produced from naphthylglycines by fusing with alkali and subsequent oxidation according to method (1*a*) for indigo blue (B. **26,** 2547). Also from the *naphthindoxylic acid esters* obtained from naphthyl-amino-malonic acid esters (B. **32,** 1236).

In conc. sulphuric acid, indigo dissolves with a green colour. Only after prolonged heating of the solution does **indigo monosulphonic acid,** "*Phœnicinsulphuric acid,*" $C_{16}H_9N_2O_2.SO_3H$, appear, which is precipitated by water as a blue powder, and forms salts soluble in water. Indigo disulphonic and trisulphonic acids (C. 1899, II. 1052) are produced by strongly fuming sulphuric acid; the disulphonic acid forms alkali salts soluble with difficulty in salt solutions. It is used commercially under the name of *Indigo carmine* as a kind of dough. That the sulpho-groups of this acid are in the *p*-position towards the two imino-groups results from the synthesis of disulphonic acid by means of anthranilino-acetic-*p*-sulphonic acid (B. **34,** 1860).

Indigo-dicarboxylic acid, $C_{16}H_8N_2O_2(COOH)_2$ is formed from *o*-nitrophthalaldehydic acid, $C_6H_3(COOH){<}\genfrac{}{}{0pt}{}{CHO}{NO_2}$, as indigo is formed from *o*-nitro-benzaldehyde.

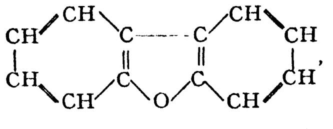
The oxidation of indigo with PbO_2, Ag_2O, or $KMnO_4$ in indifferent solvents (best on adding a little glacial acetic acid) produces **dehydro-indigo,** $C_6H_4{<}\substack{CO\\N}{>}C{-}C{<}\substack{CO\\N}{>}C_6H_4$, m.p. 210°–215° with dec., dark yellow plates. It is much more soluble in organic solvents than indigo, has a strongly oxidizing character resembling quinone, and easily reverts to indigo by reduction. It combines with two molecules of acid to light yellow salts. With sodium bisulphite it yields a beautifully crystalline addition product, $C_{10}H_8N_2O_2,2NaHSO_3+2H_2O$, of a brilliant canary colour, from which halogenated indigotins are obtained by halogenation in aqueous solution and subsequent decomposition of the resulting bisulphite compounds by boiling in dilute acids (B. **42,** 3642, 3653).

Indigo white, $C_{16}H_{12}N_2O_2$, is obtained by the reduction of indigo blue with Zn dust and alkali, hydrosulphite, or electrolysis (C. 1899, II. 235). It can be precipitated from its alkaline solution by hydrochloric acid (air being excluded) as a white crystalline powder, soluble in alcohol, ether, and the alkalies, with a yellowish colour. As it results from indigo by the addition of two hydrogen atoms, and because of its phenol-like nature, it is represented by the formula of a *di-indoxyl:* $C_6H_4{<}\substack{C(OH)\\NH}{>}C{-}C{<}\substack{C(OH)\\NH}{>}C_6H_4$. It rapidly re-oxidizes to indigo blue by exposure to the air. On acyl derivatives of indigo white, see B. **34,** 1858; **36,** 2762.

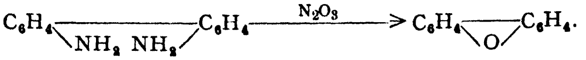
Indigo red and *indigo purpurin* are isomerides of indigo blue. The first occurs in commercial indigo, while the second is produced, together with indigo, from isatin chloride.

Indirubin, the indogenide of *pseudo*-isatin, and *indin,* formed from isatide by fusion with caustic potash, or from dioxindole, are identical with indigo purpurin (B. **28,** 540).

8. **Dibenzofuran, diphenylene oxide,**



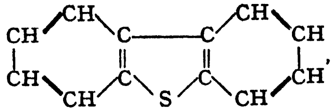
melting at 81° and boiling at 288°, occurs in small quantities in "stubb-fat," and may be obtained synthetically (1) by distilling phenyl phosphate with lime; (2) by the same treatment of phenol with lead oxide; (3) on conducting phenyl ether through tubes heated to redness; (4) by decomposing the diazo-derivative of *o*-amino-phenyl ether with sulphuric acid (compare B. **29,** 1876); and best by the action of dilute acids upon the tetrazo-compound of *o*-diamino-diphenyl (B. **25,** 2746):

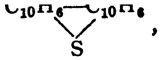


$$C_6H_4\underset{NH_2\quad NH_2}{\overline{\qquad\qquad}}C_6H_4 \xrightarrow{N_2O_3} C_6H_4\underset{O}{\overline{\quad\;}}C_6H_4.$$

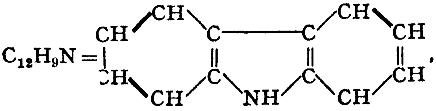
Bromine converts diphenylene oxide into **dibromodiphenylene oxide,** melting at 185°. Fuming nitric acid changes to **dinitrodiphenylene oxide,** melting at 200°. **Diaminodiphenylene oxide,** melting at 188°, yields valuable substantive azo-dyes. **Acetyldiphenylene oxide** melts at 81° (see B. **24,** R. 744).

9. **Dibenzothiophen, diphenylene sulphide,**



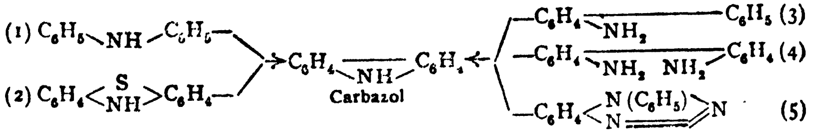
melting at 97° and boiling at 333°, is produced when phenyl disulphide, $(C_6H_5)_2S_2$, and phenyl sulphide, $(C_6H_5)_2S$, are distilled through tubes heated to redness. Chromic acid oxidizes it, in contradistinction to thiophen, to **diphenylene sulphone,** $(C_6H_4)_2SO_2$, melting at 230°. **Dinaphthothiophen,**  $\underset{S}{C_{10}H_6—C_{10}H_6}$, melting at 147°, is constituted analogously to dibenzothiophen. It results when concentrated sulphuric acid acts upon dioxydinaphthylene sulphide (B. **27,** 3002).

10. **Dibenzopyrrole, diphenyleneimine** or **carbazole,**

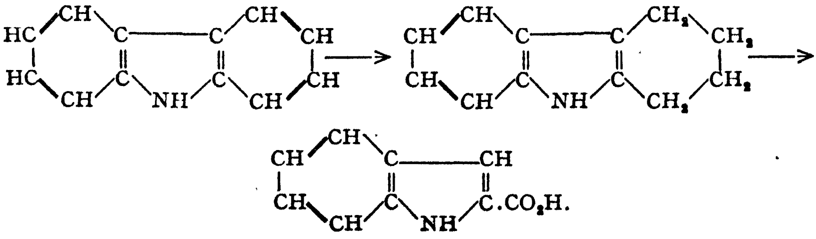


melting at 238° and boiling at 351°, occurs in crude anthracene. It is withdrawn from it as potassium carbazole by fusion with caustic potash. It may be synthesized:

(1) By conducting diphenylamine through tubes heated to redness; (2) by heating thiodiphenylamine with copper in powder form; (3) by distilling *o*-aminodiphenyl with lime (B. **24,** 306); (4) by heating *o*-diaminodiphenyl with acids (B. **25,** 133); (5) from *o*-aminodiphenylamine through the diazo-compound. The phenylbenzíminazole, produced at first, yields, when exposed to a higher temperature, nitrogen and carbazole (A. **291,** 16):



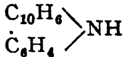
Behaviour.—Carbazole gives the *pine-shaving reaction* and the blue coloration with sulphuric acid and isatin, just the same as the pyrrole and most of the indole derivatives. This and its other deportments would justify the conclusion that it is dibenzopyrrole or benzoindole—*e.g.*, tetrahydrocarbazole, when fused with potassium hydroxide, breaks down into *α*-indolecarboxylic acid:



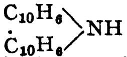
Carbazole, like pyrrole, is a very feeble base. It forms a stable salt with picric acid; the *picrate* melts at 182°. Nitrous acid converts it into *nitrosocarbazole*, $(C_6H_4)_2N.NO$, melting at 84°. Heated with potash it yields *potassium carbazole*, $(C_6H_4)_2NK$. Alkyl iodides convert this into *N*-**methylcarbazole,** $(C_6H_4)N.CH_3$, melting at 87°, and *N*-**ethylcarbazole,** $(C_6H_4)_2N.C_2H_5$, melting at 68°. Carbazole and acetic anhydride yield *N-acetylcarbazole*, $(C_6H_4)_2N.COCH_3$, melting at 69°. Chlorine produces various *chlorcarbazoles;* nitric acid, *nitrocarbazoles* (A. **202,** 27; B. **29,** R. 292, 650, 1112). When carbazole and oxalic acid are fused together, **Tricarbazylcarbinol** or **Carbazole Blue** results. **Dimethyl carbazole,** $(CH_3.C_6H_3)_2NH$, melting at 364°, is made from *o*-toluidine by the pyrogenic method (B. **29,** 2594).

Hydrocarbazoles.—**Tetrahydrocarbazole,** $C_6H_4\left<\begin{array}{c}\overline{\qquad}\\ NH\end{array}\right>C_6H_8$, melting at 119°, results from the reduction of carbazole, as well as from the phenylhydrazone of ketohexamethylene, analogously to Fischer's indole synthesis. It behaves like an alkyl indole (compare hydronaphthalenes). When acted upon by alkyl iodides or with chloroform, it passes in a similar manner into acridine derivatives, just as the indoles become quinoline compounds (Gaz. chim. ital. **24,** 111). By the potash fusion it, like the alkyl indoles, yields indolecarboxylic acid (see above and B. **26,** 2006). **Tetrahydrocarbazolecarboxylic Acid,** $C_6H_4\left<\begin{array}{c}\overline{\qquad}\\ NH\end{array}\right>C_6H_7.COOH$, melting at 230°, is formed from the phenylhydrazone of ketohexahydrobenzoic acid (B. **22,** 2185). **Hexahydrocarbazole,** $C_6H_4\left<\begin{array}{c}\overline{\qquad}\\ NH\end{array}\right>C_6H_{10}$, melting at 99° and boiling at 267°, is a strong base (A. **163,** 352), just like the pyrrole and indole hydrides.

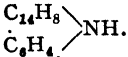
The following are similar to carbazole in method of production and in their behaviour:


$\left.\begin{array}{l}C_{10}H_6\\ \dot{C}_6H_4\end{array}\right>NH$

Naphtho-benzopyrrole.


$\left.\begin{array}{l}C_{10}H_6\\ \dot{C}_{10}H_6\end{array}\right>NH$

Dinaphtho-pyrrole.


$\left.\begin{array}{l}C_{14}H_8\\ \dot{C}_6H_4\end{array}\right>NH.$

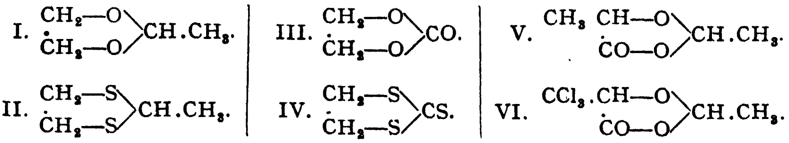
Phenanthro-benzopyrrole.

Of the three possible isomers [1,2]-, [2,1]-, and [2,3]-**naphthobenzopyrrole,** m.p. 225°, 135°, and 330° respectively, the first two have been obtained from *α*- and *β*-naphthol with phenylhydrazine; the second also from 2,3-hydroxy-naphthoic acid with phenylhydrazine and subsequent elimination of CO_2 (C. 1901, II. 427); the last is found in crude anthracene. *Dinaphthopyrroles* are known, with melting-points at 155° [*sym.* 1,2 isomer], 231° [1,2,2′,1′], and others (compare C. 1903, I. 588, 883).

Phenanthro-benzopyrrole, *αβ*-diphenylene indole, m.p. 189; **phenanthro-naphthopyrroles,** m.p. 220° and 225°.

POLYHETERO-ATOMIC FIVE-MEMBERED RINGS.

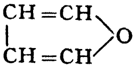
The acetals and mercaptals of ethylene glycol—*e.g.*, ethylene ethylidene ether (I.), and *ethylene ethylidene sulphide* (II.) (I. 317, 324)—are five-membered rings with two O- or S-atoms. This is also the case with the ethylene esters of the carbonic acid group—*e.g.*, *carbonic ethylidene ester* (III.), and *trithiocarbonic ethylene ester* (IV.) (I. 434), the ethylidene esters of α-oxyacids—*e.g., lactic ethylidene ester* (V.), and *chloralide*, its chlorination product (VI.).



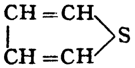
Several five-membered cyclic esters and amido-derivatives have also been obtained from phosphoric acid (see B. **31,** 1111, etc.).

AZOLES.

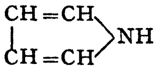
There is another group, of greater importance than those discussed. It comprises the bodies containing polyhetero-atomic five-membered rings, which are embraced under the name *azoles* (A. **249,** 1; B. **24,** 2824; B. **22,** R. 737). They contain as hetero-atoms N and O, N and S, or only N-atoms. We may view them as derived from the monohetero-atomic rings—furan, thiophen, and pyrrole—by the replacement of methine groups by N-atoms, whereby, as previously indicated, the stability of the ring is very slightly affected. Viewing the numerous classes of bodies belonging here as nitrogen substitution products of the monohetero-atomic rings, we arrive at a natural systematization of the former, and also reach a simple nomenclature for them, which in many instances is quite similar to the names which have become peculiar to the individual groups. The individual azoles, depending upon whether they are derived from furan, thiophen, or pyrrole, by the replacement of one, two, or three CH-groups by N-atoms, are designated as furo-monazoles, thio-diazoles, pyrro-triazoles. To distinguish the metameric rings the methine groups of furan, etc., are termed [a], [a$_1$], [b], [b$_1$] $\begin{array}{l}[b]CH=CH[a]\\ \;|\qquad\qquad >R\\ [b_1]CH=CH[a_1]\end{array}$, and the substituents as α, α_1, β, β_1 (p. 13), so that we distinguish *furo*-[a]-*monazole*, *furo*-[b]-*monazole*, *pyrro*-[aa$_1$]-*diazole*, *pyrro*-[ab]-*diazole*, *pyrro*-[ab$_1$]-*diazole*, etc. Retaining the names of the individual bodies and the groups introduced by their discoverers, there will in the following pages be placed at the beginning of each individual group the names resulting from the introduction of the nomenclature just described. This will render the constitution and the position of the azoles in the system, which follows, very evident:



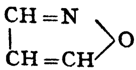
Furan.



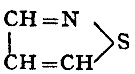
Thiophen.



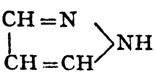
Pyrrole.



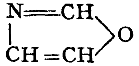
Furo-[a]-monazole,
Isoxazole.

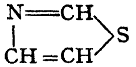


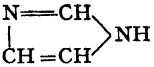
Thio-[a]-monazole,
Comp. Benzisothiazol

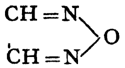


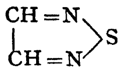
Pyrro-[a]-monazole,
Pyrazole.

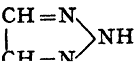

Furo-[b]-monazole, Oxazoles.

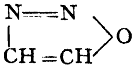

Thio-[b]-monazole, Thiazoles.

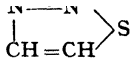

Pyrro-[b]-monazole, Imidazoles, Glyoxalines.

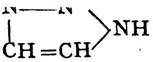

Furo-[aa$_1$]-diazole, Furazans.

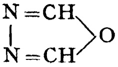

Thio-[aa$_1$]-diazoles, Piazthioles.

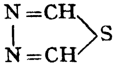

Pyrro-[aa$_1$]-diazole, Osotriazole.

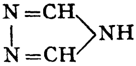

Furo-[ab]-diazole, Anhydrides of *o*-Diazophenols.

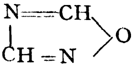

Thio-[ab]-diazole, Phenylenediazosulphides.

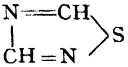

Pyrro-[ab]-diazole.

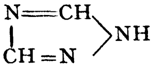

Furo-[bb$_1$]-diazole, Oxydiazoles.

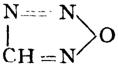

Thio-[bb$_1$]-diazole, Thiodiazoles.

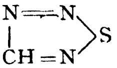

Pyrro-[bb$_1$]-diazole.

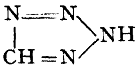

Furo-[ab$_1$]-diazole.

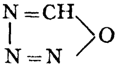

Thio-[ab$_1$]-diazole.

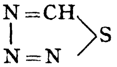

Pyrro-[ab$_1$]-diazole, Triazoles.

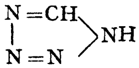

Furo-[aa$_1$b]-triazole.

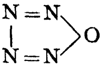

Thio-[aa$_1$b]-triazole.

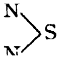

Pyrro-[aab$_1$]-triazole, Tetrazoles.

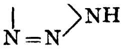

Furo-[abb$_1$]-triazole (Comp. B. 29, 2492).


Thio-[abb$_1$]-triazoles.


Pyrro-[abb$_1$]-triazole, Tetrazoles.

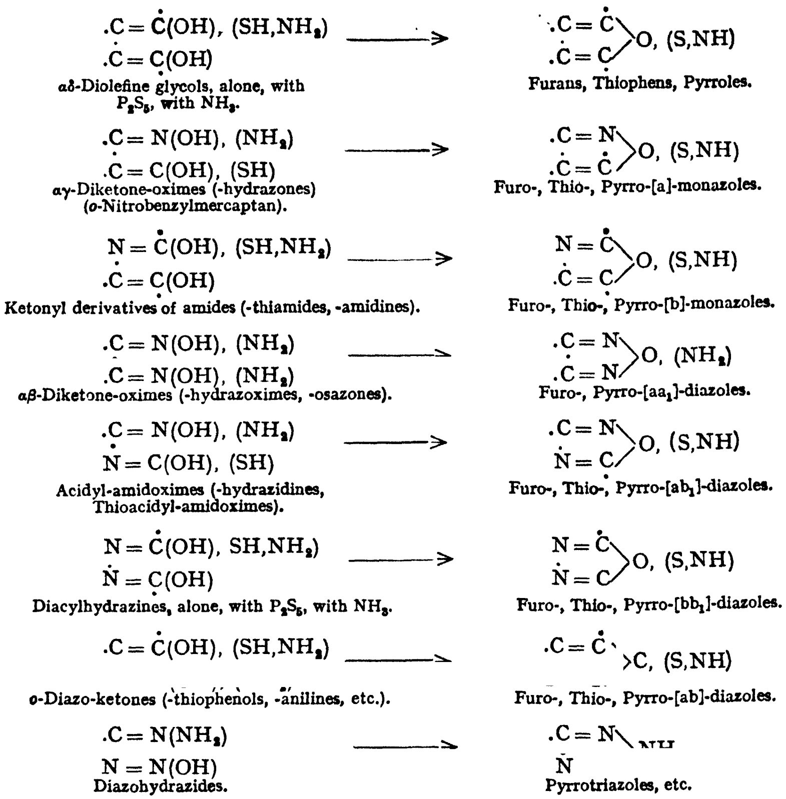

Furotetrazole.


Thiotetrazole.


Pentazole.

The parent substances of all the rings just given have not been prepared. In most instances, however, their next homologues are known; in some cases only the *benzo*-derivatives. Only single representatives of the furo- and thiotriazoles are known at the present time. It is, however, not impossible that by synthesis these rings, consisting mainly of inorganic elements, may be multiplied and the system extended. Indeed, we may succeed to such a degree that the purely inorganic rings—*e.g.*, those constructed from four N-atoms and an NH-group—will be prepared. This would be a ring homologue of hydrazoic acid. From the standpoint of a ***nitrogen chemistry*** the C-containing rings could be as readily evolved from the nitrogen ring by replacing the N-atoms with CH-groups, as was suggested above in the reverse case.

The derivation of these ring systems from furan, thiophen, and pyrrole, enables us to regard the chief formation methods of the azoles as the analogues of the general formation of furans, thiophens, and pyrroles from αδ-diketones and αδ-diolefine glycols. The ultimate azole generators are obtained by making the "azo-substitution" in the 1,4-diolefine glycol chain—*e.g.:*


αδ-Diolefine glycols, alone, with P_2S_5, with NH_3.
Furans, Thiophens, Pyrroles.
αγ-Diketone-oximes (-hydrazones) (o-Nitrobenzylmercaptan).
Furo-, Thio-, Pyrro-[a]-monazoles.
Ketonyl derivatives of amides (-thiamides, -amidines).
Furo-, Thio-, Pyrro-[b]-monazoles.
αβ-Diketone-oximes (-hydrazoximes, -osazones).
Furo-, Pyrro-[aa₁]-diazoles.
Acidyl-amidoximes (-hydrazidines, Thioacidyl-amidoximes).
Furo-, Thio-, Pyrro-[ab₁]-diazoles.
Diacylhydrazines, alone, with P_2S_5, with NH_3.
Furo-, Thio-, Pyrro-[bb₁]-diazoles.
o-Diazo-ketones (-thiophenols, -anilines, etc.).
Furo-, Thio-, Pyrro-[ab]-diazoles.
Diazohydrazides.
Pyrrotriazoles, etc.

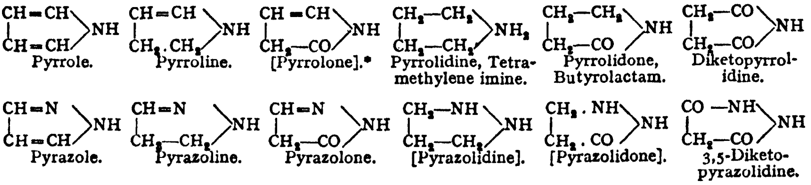
It is useful to compare the above scheme with the processes detailed below.

The numerous and important *pyrazoles*, together with their benzo-derivatives, the *indazoles*, consisting of dihetero-atomic rings, will be next discussed; then will follow the *isoxazoles*, with their *benzo*-derivatives, the *benzisoxazoles*. After this will appear the glyoxalines or *iminazoles*, the *oxazoles*, and the *thiazoles*, sometimes in conjunction with their benzo-derivatives, which it is customary to consider under the name of *anhydro-bases*, because they are formed from *o*-diamines, *o*-aminophenols, and *o*-aminothiophenols with carboxylic acids by the exit of water. In the trihetero-atomic rings, again, the groups of the pyrrodiazoles or *triazoles* are placed first; the *azimides* and *pseudo-azimides* belong to their benzo-derivatives. Attached to these are the furodiazoles: the *furazans, diazo-oxides, oxydiazoles, azoximes;* and the *thiodiazoles: azosulfimes, thiodiazolines, piazothioles* (*piaselenoles*), *thio*-[ab]-*diazoles*, and *phenylenediazosulphides*. The *triazsulpholes* and *tetrazoles* conclude the list.

1. PYRAZOLE OR PYRRO-[a]-MONAZOLE GROUP.

Pyrazole, $C_3H_4N_2$, may be regarded as derived from pyrrole by replacement of a methine-group adjacent to an NH-group by nitrogen —*pyrro*-[a]-*monazole* (see above). See 3-methylpyrazole for details in regard to the constitution of pyrazole. There are a *dihydropyrazole* or *pyrazoline* and a *tetrahydropyrazole* or *pyrazolidine* corresponding to the di- and tetrahydropyrrols.

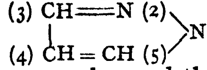
Keto-substitution products of these hydrogenized pyrazoles are ketopyrazoline or *pyrazolone*, among the derivatives of which is the febrifuge *antipyrine*, ketopyrazolidine or *pyrazolidone*, and *diketopyrazolidine*, corresponding to the butyrolactam or pyrrolidone and succinimide. The subjoined diagram indicates the relations existing between these pyrazole and the pyrrole derivatives:


Pyrrole. Pyrroline. [Pyrrolone].* Pyrrolidine, Tetramethylene imine. Pyrrolidone, Butyrolactam. Diketopyrrolidine.

Pyrazole. Pyrazoline. Pyrazolone. [Pyrazolidine]. [Pyrazolidone]. 3,5-Diketopyrazolidine.

Pyrazole, $C_3H_4N_2$, melting at 70° and boiling at 187°, results from epichlorhydrin, hydrazine hydrate, and zinc chloride (B. **23,** 1105). A better method consists in splitting off CO_2 from its carboxylic acids (B. **26,** R. 282), or in the action of bromine upon pyrazoline (B, **29,** 775). It is a feeble base; its salts are unstable. It does not combine with methyl iodide. An ammoniacal silver solution precipitates *silver pyrazole*, $C_3H_3H_2Ag$, corresponding to potassium pyrrole. The *platinum double salt*, $(C_3H_4N_2.HCl)_2PtCl_4$, at 200°–210°, loses four molecules of hydrochloric acid and becomes $(C_3H_3N_2)_2PtCl_2$ (B. **26,** R. 185). N-*Acetylpyrazole*, boiling at 156°, and N-*benzoylpyrazole*, boiling at 281°, result from the action of acetyl chloride and benzoyl chloride upon pyrazole (B. **28,** 716).

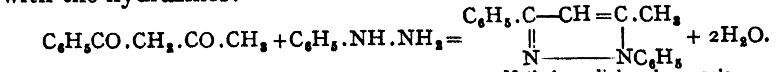
The pyrazole derivatives are designated in the following manner:


(3) CH==N (2) NH (1) (4) CH = CH (5)

(or *N*); the numbering proceeds from the imine group, beyond the second nitrogen atom.

1. *Homologous Pyrazoles* are formed:

(1) From the hydrazones of the β-diketones and β-ketone aldehydes or hydroxymethylene ketones. As a rule, the reactions proceed smoothly with the elimination of water, when the ketones are digested with the hydrazines:



$$C_6H_5CO.CH_2.CO.CH_3 + C_6H_5.NH.NH_2 = \begin{array}{l} C_6H_5.C—CH=C.CH_3 \\ \;\;\;\;\;\| \qquad\quad | \\ \;\;\;\;N———NC_6H_5 \end{array} + 2H_2O$$

Benzoyl acetone. 5-Methyl-1,3-diphenyl pyrazole.

By this procedure the unsymmetrical β-diketo-compounds yield two isomeric pyrazoles; this is because the two possible hydrazones are formed. In the example cited the 1,5,3-*body* is produced, together with 1,3,5-diphenylmethylpyrazole. The oxalyldiketones (I. 597; II. 640) and phenylhydrazine yield the *bis-phenylalkylpyrazoles:*

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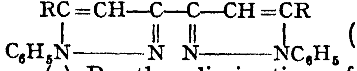
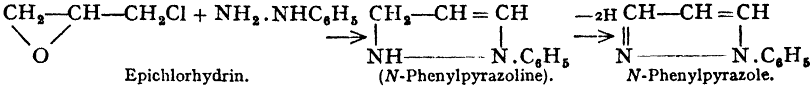
* The parent substances, enclosed in brackets, are only known in the derivatives.



(A. **278,** 295).

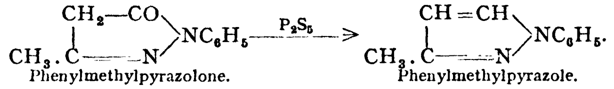
(2) By the elimination of carbon dioxide from the homologous pyrazolecarboxylic acids.

(3) By the loss of hydrogen from the pyrazoline. Frequently, in reactions where pyrazolines may well be expected pyrazoles appear. This is true of the interaction of the hydrazines and epichlorhydrin:



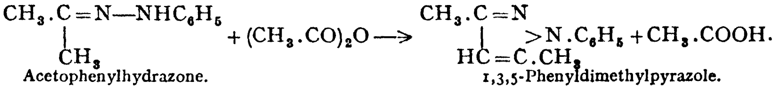
Epichlorhydrin. (*N*-Phenylpyrazoline). *N*-Phenylpyrazole.

(4) Pyrazoles also result upon distilling pyrazolones or pyrazolidones with zinc dust or P_2S_5 (B. **26,** 103), or on heating them with phosphorus tribromide under pressure (A. **352,** 322).



Phenylmethylpyrazolone. Phenylmethylpyrazole.

(5) Certain hydrazones of mono-ketones yield pyrazoles when they are heated with acid anhydrides (Bull. Soc. Chim. [3], **11,** 115; see B. **28,** 703, Anm. 4):



Acetophenylhydrazone. 1,3,5-Phenyldimethylpyrazole.

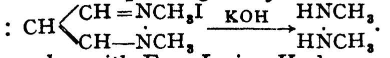
Behaviour.—The homologous pyrazoles may be arranged in three groups: (1) Pyrazoles with free imine-group; (2) *N*-alkyl substituted pyrazoles, which can be obtained from the first class (or their silver salts) by the action of alkyl iodides—best by the distillation of the iodalkylates (B. **28,** 716) with an excess of alkyl iodide—or from β-diketones and alkylhydrazines; (3) *N*-phenyl substituted pyrazoles, which are made through the phenylhydrazines, and are chiefly distinguished by their stability and power of crystallization.

All pyrazole homologues are feeble bases. They form double salts with silver nitrate, mercuric chloride, and platinic chloride. The platinum double salts, like that of pyrazole, part with 4HCl on heating, and become R_2PtCl_2 (R = the pyrazole residue). They usually combine with alkyl iodide to form ammonium compounds (see above).

Potassium permanganate oxidizes the *C*-alkyl pyrazoles to pyrazolecarboxylic acids, in contradistinction to the pyrroles, which are destroyed by this reagent (B. **22,** 172).

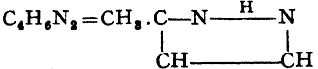
In the *N*-phenyl pyrazoles during the oxidation the phenyl group is often split off and replaced by hydrogen. This is particularly true if it be aminated. The behaviour is quite different during *reduction.* Pyrazoles with the free imine-group are but slightly altered by the reducing agents (A. **273,** 266). *N*-Phenylpyrazoles are reduced to pyrazolines (p. 83), which yield intense colorations with ferric chloride, chromates, etc. (*Knorr's pyrazoline reaction*). In more energetic reductions *trimethylenediamine derivatives* are formed by the rupture of the union between the N-members. In some *N*-phenylpyrazoles the reduction is accompanied by the splitting off of the phenyl group as benzene or some similar group.

The iodo-alkylates of the *N*-alkyl or aryl pyrazoles decompose on boiling with KHO, splitting off *symm.* dialkylhydrazines (B. **39,** 3257; **42,** 3523):



$$CH\begin{cases}CH=NCH_3I\\CH—NCH_3\end{cases}\xrightarrow{KOH}\begin{matrix}HNCH_3\\HNCH_3\end{matrix}.$$

(1) *Pyrazoles with Free Imine Hydrogen:* 3- (or 5-) **Methylpyrazole,**



$$C_4H_6N_2=CH_3.C—\overset{H}{N}—N \quad \begin{matrix}CH—CH\end{matrix}$$

(see below), is an oil boiling at 204°. It results—

(*a*) From the interaction of hydroxymethylene acetone and hydrazine.

(*b*) From its carboxylic acids.

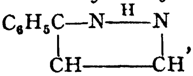
(*c*) As well from 1,3- as from 1,5-phenylmethylpyrazole by elimination of the phenyl group through oxidation (A. **279,** 217-225).

The last two methods show conclusively that 3-methylpyrazole and 5-methylpyrazole are identical. It is concluded, therefore, that pyrazole, like benzene, possesses "oscillating linkages"; the imine hydrogen atom is capable of oscillating between the two N-atoms (Knorr, A. **279,** 188). The formula presented above for pyrazole is supposed to represent this condition.

3,5-**Dimethylpyrazole,** $NH—N=C(CH_3)—CH=C(CH_3)$, melts at 107° and boils at 220°. It is obtained from acetylacetone and hydrazine, and from 1,3,5-phenyldimethylpyrazole by reduction (*elimination of the* C_6H_5-*group*) (B. **25,** R. 163, 744).

3,4,5-**Trimethylpyrazole,** $NH—N=C(CH_3)—C(CH_3)=C(CH_3)$, melting at 138° and boiling at 233°, is obtained from methylacetylacetone.

3,4,4,5-**Tetramethylpyrazole,** $N=C(CH_3)—C(CH_3)_2—C(CH_3)=N$, melting at 50°-55° and boiling at 243°, is formed from dimethylacetylacetone (A. **279,** 244, 247). 3- (or 5-) **Phenylpyrazole,**



$$C_6H_5C—\overset{H}{N}—N \quad CH—CH$$

, melting at 78°, is formed from benzoylacetaldehyde (B. **28,** 696).

Isomeric 4-**Phenylpyrazole,** melting at 228°, is obtained from 1,4-phenylpyrazolecarboxylic acid (A. **279,** 254; B. **27,** 3247; **28,** 223, 699); 3,5-**Phenylmethylpyrazole,** $NH—N=C(CH_3)—CH=C(C_6H_5)$, melting at 128° and boiling at 317°, has been prepared from benzoylacetone (A. **279,** 248), as well as from phenylmethylisoxazole, on heating with alcoholic ammonia (B. **28,** 2952).

(2) N-*Alkyl Pyrazoles: N*- (or 1-) **Methylpyrazole,** $C_3H_3N_2.CH_3$, boiling at 127°, is formed in the interaction of silver pyrazole and methyl iodide (B. **26,** R. 281; **28,** 716). 1,3-**Dimethylpyrazole,**

$C_3H_2(CH_3)N_2.CH_3$, boils at 150° (A. **279,** 231); 1,3,5-**Trimethylpyrazole,** $C_3H(CH_3)_2N_2CH_3$, melting at 37° and boiling at 170°, crystallizes in combination with one molecule of chloroform. 1,3,4,5-**T** **pyrazole,** $C_3(CH_3)_3N_2CH_3$, boils at 190° to 193°. These compounds are also formed from acetylacetone and methylacetylacetone by the action of methylhydrazine (A. **279,** 232, 235).

(3) N-*Phenyl Pyrazoles.*—*N*- (or 1-) **Phenylpyrazole,** $C_3H_3N_2.C_6H_5$, melting at 11° and boiling at 246°, with sp. gr. 1.1125, is obtained from epichlorhydrin and phenylhydrazine (see above), as well as from its carboxylic acids. It yields, upon reduction, phenylpyrazoline, together with phenyltrimethylenediamine. *N*-**Tolylpyrazole,** $C_3H_3N_2.C_7H_7$, melting at 33° and boiling at 259°, yields in like manner tolyltrimethylenediamine (Gaz. ch. ital. **18,** 354). 1-**Phenyl**-3-**methylpyrazole** melts at 37° and boils at 255°. Its *iodomethylate* melts at 144°. The first body is derived from phenylmethylpyrazolone (A. **238,** 203; B. **24,** 648), as well as from hydroxymethylene acetone, together with the isomeric 1-**Phenyl**-5-**methylpyrazole,** $C_6H_5\overline{N—N=CH—CH=C}(CH_3)$. This is an oil boiling at 255°. Its *iodomethylate* melts with decomposition at 296°. 1-**Phenyl**-4-**methylpyrazole,** $C_6H_5\overline{N—N=CH—C(CH_3)=C}H$, boiling at 266°, is formed by a rearrangement of the iodomethylate of 1-phenylpyrazole (B. **26,** R. 327). 1-**Phenyl**-3,5-**dimethylpyrazole,** $C_3(CH_3)_2HN_2.C_6H_5$, boiling at 273°, is obtained from acetyl acetone. Upon reduction it yields dimethylpyrazole and benzene, together with 1-*Tetrahydrophenyl*-3,5-*dimethylpyrazole,* which, by oxidation, is decomposed into dimethylpyrazole and adipic acid (B. **26,** R. 246). 1-**Phenyl**-3,4-**dimethylpyrazole,** boiling at 278°, results from hydroxymethylene methyl ethyl ketone, $CHOH:C(CH_3).CO.CH_3$ (B. **25,** R. 943). 1,3-**Diphenylpyrazole,** $C_3H_2(C_6H_5)N_2.C_6H_5$, melting at 56° and boiling at 337°, is obtained from benzoylacetaldehyde (B. **21,** 1135); 1,5-**Diphenylpyrazole,** melting at 54° and boiling at 340°, is derived from its carboxylic acid (B. **25,** 3145); 1,3,5-**Triphenylpyrazole,** $C_3H(C_6H_5)_2.N_2.C_6H_5$, melting at 212°, is made from its carboxylic acid (B. **26,** 1881). See A. **289,** 332, for the production of 1,3,4-**triphenylpyrazole,** melting at 185°, by the decomposition of 1,3,4,6-**tetraphenyldihydropyridazine** (see A. **289,** 332).

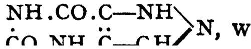
2. **Haloid-, Nitro-, Nitroso-, Amino-pyrazoles, Benzeneazo-pyrazoles, Pyrazole-sulphonic Acids.**—The halogens replace the hydrogen atoms in pyrazole. Bromine reacts most readily. The halogen atoms in the 4-position are most securely combined. Chloropyrazoles are formed by the action of phosphorus oxychloride upon pyrazolone. In the sulphonation and nitration of pyrazole the NO_2 and SO_3H-groups also enter the nucleus. *N*-Phenyl pyrazoles are nitrated and sulphonated in the phenyl residue. *N*-Phenylpyrazolesulphonic acids have also been prepared by the introduction of phenylhydrazine sulphonic acids in the pyrazole syntheses (A. **278,** 296). In the nitropyrazoles the basic character of the pyrazoles disappears. They are acids, which form stable sodium, potassium, etc., salts.

The amino-pyrazoles result in the reduction of the corresponding nitro-bodies. They resemble the aromatic amines in their deportment.

They have also been obtained by the action of hydrazines upon the nitriles of β-ketone-carboxylic acids and upon malononitrile; also by disintegrating the pyrazole carboxylic acids by way of the hydrazides, azides, and urethanes by the method of Curtius. Nitroso- and benzeneazo-pyrazoles are formed synthetically from *iso*nitroso- and benzeneazo-β-diketones with hydrazines.

4-**Chloropyrazole,** $C_3H_3ClN_2$, m.p. 77°, is formed by the action of sulphuryl chloride upon pyrazole in ether solution (C. 1906, II. 684). 4-**Bromopyrazole,** $C_3H_3BrN_2$, m.p. 97°; 3-**Methylbromopyrazole,** m.p. 67° (A. **279,** 227); 1,3,5-**Triphenylbromopyrazole,** m.p. 142°; 1-**Phenyltribromopyrazole,** m.p. 107°; 4-**Iodopyrazole,** $C_3H_3IN_2$, m.p. 108° (also from pyrazole-4-diazoniumchloride and KI (B. **26,** R. 281; **37,** 3522); 1,4-**Phenylchloropyrazole,** m.p. 76° (A. **318,** 21); 3,5-**Phenylchloropyrazole,** m.p. 142° (A. **352,** 159); 1,5-**Phenylchloropyrazole,** 1-**Phenyl**-3-**methyl**-5-**chloropyrazole,** b.p.$_9$ 142°, and 1-**Phenyl**-3,5-**dichloropyrazole,** m.p. 26°, b.p.$_{16}$ 171°, from 1-Phenyl-5-pyrazolone, 1,3-Phenylmethylpyrazolone and phenyloxypyrazolone (B. **31,** 3003; A. **320,** 28). 1-**Phenyl**-5-**methyl**-3-**chloropyrazole,** b.p.$_{15}$ 170°, from 1,5-Phenylmethyl-3-pyrazolone.

4-**Nitropyrazole,** $C_3H_3(NO_2)N_2$, m.p. 162°, is also obtained synthetically from the results of the action of hydrazine upon nitromalonic aldehyde; also 1-**phenyl**-4-**nitropyrazole,** m.p. 127°, from phenyl hydrazine and nitromalonic aldehyde (C. 1899, II. 609). 3-**Methyl**-4-**nitropyrazole,** m.p. 134°, b.p. 325°, from methylpyrazole or 3-methyl-5-pyrazolecarboxylic acid with nitrosulphuric acid (A. **279,** 228). 4-**Nitro**-1,3,5-**trimethylpyrazole,** m.p. 57°. 3,5-**Dimethyl**- and 1,3,5-**Phenyldimethyl**-4-**nitrosopyrazole,** $C_3(CH_3)_2(NO)N_2H$, blue needles, m.p. 128°, and $C_3(CH_3)_2(NO):N_2(C_6H_5)$, green flakes, m.p. 94°, are formed from *iso*nitroso-acetylacetone (Vol. I.) with hydrazine and phenylhydrazine. The latter is oxidized by nitric acid to 1,3,5-**phenyl-dimethyl**-4-**nitropyrazole,** m.p. 103° (A. **325,** 192; B. **40,** 664).

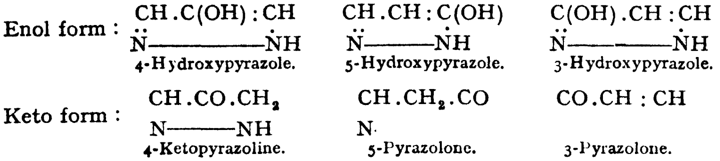
4-**Aminopyrazole,** $C_3H_3(NH_2)N_2$, m.p. 81°, sublimes easily. It is prepared by reducing 4-nitropyrazole with zinc dust and acetic acid; also by splitting up *iso*xanthine,  $\left.\begin{array}{l} NH.CO.C\text{—}NH \\ \dot{C}O.NH.\ddot{C}\text{—}CH \end{array}\right\rangle N$, which is formed from amino-methyluracil with N_2O_3 (A. **323,** 281; B. **37,** 3520). It is easily soluble in water, and rapidly absorbs atmospheric oxygen, especially in alkaline solution, and acquires a dark colour. More stability is shown by 3(5)-**amino-pyrazole,** b.p. 282°, and 3,5-**di-amino-pyrazole** (dibenzoate, m.p. 207°), obtained by breaking up the pyrazole carboxylic azides. 4-**Amino**-1,3,5-**trimethylpyrazole,** m.p. 103°, by reduction of nitro-trimethyl-pyrazole. With nitrous acid the amino-pyrazoles form remarkably stable diazonium salts, not decomposed by boiling in water, which resemble the aromatic diazo-compounds in their transformations, and may, for instance, be converted into azo-dyes by combining them with anilines, phenols, etc. Other benzeneazo-pyrazoles like 1-**Phenyl**- and 1,5-**Phenylmethyl**-4-**benzeneazopyrazole,** $C_6H_5N:NC_3H_2N_2.C_6H_5$, m.p. 124°, and $C_6H_5N:NC_3H(CH_3)N_2.C_6H_5$, m.p. 112°, have been obtained synthetically from the benzeneazo-compounds of malonic dialdehyde and aceto-acetic aldehyde with phenyl hydrazine; while the 1,3-**phenylmethyl**-4-**benzeneazo-pyrazole,** m.p. 126°, has been obtained from benzeneazo-phenyl-methyl-pyrazolone (B. **36,** 3596, 3669). 1,5,3-**Diphenyl-methyl-4-benzeneazo-pyrazole,** m.p. 136°, from phenyl methyl triketone with phenylhydrazine (B. **35,** 3317). 1-**Phenyl-3-methyl-5-azopyrazole,** m.p. 62°, from phenyl hydrazinopyrine by oxidation with HgO and subsequent heating (B. **42,** 2765).

1,3-**Phenylmethyl-5-amino-pyrazole,** m.p. 116°, from diaceto-nitrile with phenylhydrazine, is also formed by superheating antipyrine chloride with ammonium carbonate (A. **339,** 134).

1-**Phenyl-3,4-ethylmethyl-5-aminopyrazole,** m.p. 81°, from methylpropionylacetonitrile, $C_2H_5COCH(CH_3)CN$, and phenylhydrazine (Bull. soc. ch. [4], **4,** 647).

Methylpyrazolesulphonic acid, $C_3H_2N_2(CH_3)(SO_3H)$, m.p. 258°, from methylpyrazole with fuming sulphuric acid (A. **279,** 230).

3. **Hydroxypyrazoles.**—The hydroxypyrazoles are desmotropic with the ketopyrazolines or pyrazolones:



Enol form: $\begin{array}{l}CH.C(OH):CH\\ \ddot{N}\text{————}NH\end{array}$ 4-Hydroxypyrazole. $\begin{array}{l}CH.CH:C(OH)\\ \ddot{N}\text{———}NH\end{array}$ 5-Hydroxypyrazole. $\begin{array}{l}C(OH).CH:CH\\ N\text{————}NH\end{array}$ 3-Hydroxypyrazole.

Keto form: $\begin{array}{l}CH.CO.CH_2\\ N\text{———}NH\end{array}$ 4-Ketopyrazoline. $\begin{array}{l}CH.CH_2.CO\\ N\end{array}$ 5-Pyrazolone. $CO.CH:CH$ 3-Pyrazolone.

In the 4-hydroxypyrazoles the hydroxyl form seems to be the more stable. They easily yield urethanes and benzoic acid esters with phenyl *iso*cyanate and with benzoyl chloride, and they yield benzene-azo- and *iso*nitroso-compounds with diazo-benzo-salts and with N_2O_3 (A. **313,** 1). But the 3- and 5-pyrazolones also yield on alkylation, besides isomeric *N*-alkyl derivatives (antipyrines), alkoxypyrazoles, and with acid halides esters of hydroxypyrazoles. With alkyl iodides, the alkoxypyrazoles give addition products which can also be obtained from the antipyrines with alkyl iodide. These revert to antipyrines on slightly warming alone or with alkali. The acid esters of the oxypyrazoles also give alkyl iodide addition products which, on splitting up, yield antipyrines (J. pr. Ch. [2], **54,** 177; **55,** 145; A. **293,** 42; compare also B. **32,** 2399). Alkoxypyrazoles are also obtained by elimination of H_2O from the hydrazones of β-ketone acid esters by suitable reagents.

4-**Hydroxypyrazole,** m.p. 118°, from its carboxylic acid, with benzoyl chloride and soda, gives 1,5-**dibenzoxypyrazole,** m.p. 109°, and with methyl iodide the iodo-methylate of 1-methyl-4-oxypyrazole. 1-**Phenyl-4-hydroxypyrazole,** m.p. 120°, from its carboxylic acid, gives with phenyl *iso*cyanate, $C_3(OCONHC_6H_5)H_2N_2.C_6H_5$, m.p. 168°. 3,5-**Dimethyl** and 3,5-**phenyl-methyl-4-hydroxypyrazole,** m.p. 173° and 188° respectively, from dimethyl and phenyl methyl triketone with hydrazine (B. **35** 3313, 3318).

1-**Phenyl-5-ethoxypyrazole** is obtained from its carboxylic ester, the condensation product of oxal-acetic ester phenylhydrazone by means of $ZnCl_2$ (B. **26,** R. 550). On saponification of the ethoxy-group with HCl it passes into *N*-**phenylpyrazolone,** m.p. 118° (B. **27,** 407). 1-**Phenyl-3-methyl-5-methoxypyrazole,** b.p. 240°, is formed from phenylmethylpyrazolone with diazo-methane (B. **28,** 1626) or methyl iodide and sodium methylate, besides the isomeric antipyrine;

also from aceto-acetic methyl ester with phenylhydrazine and HCl. On heating to 250° it is transposed into antipyrine (C. 1898, I. 812). Its iodo-methylate, also from antipyrine and methyl iodide, also yields pure antipyrine on boiling with caustic soda (A. **293,** 17).

1-**Phenyl-3-methyl-5-ethoxypyrazole,** m.p. 38°, b.p. 301°, from aceto-acetic ethyl ester phenylhydrazone with acetyl chloride and excess of HCl, gives on saponification phenylmethylpyrazolone, and with Na and alcohol phenylmethylpyrazoline (B. **28,** 627, 635, 706). The two last ethers have also been obtained by removal of CO_2 from phenyl-methyl-carbomethoxy- and -carbethoxy-pyrazolones, the products of the action of chloro-carbonic methyl and ethyl esters upon phenyl-methylpyrazolone (J. pr. Ch. [2], **54,** 180; **55,** 149).

1-**Phenyl-5-methyl-3-methoxypyrazole,** b.p. 274°, from 1,5-phenyl-methyl-3-pyrazolone with methyl iodide and sodium methylate (A. **338,** 282).

4. **Pyrazole ketones,** or *C-Acyl Pyrazoles,* are formed, like the thiophen, indole, and pyrrole ketones, on heating the pyrazoles with acid chlorides:

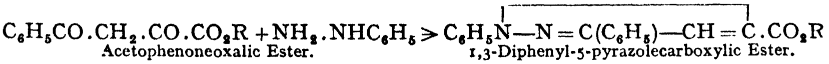
(1) 1-**Phenyl-4-acetyl-pyrazole,** $C_3(COCH_3)H_2N_2.C_6H_5$, melting at 122°. Its *oxime* melts at 130° and its *phenylhydrazone* at 143° with decomposition. 1-**Phenylbenzoylpyrazole,** $C_3(COC_6H_5)H_2N_2C_6H_5$, melts at 123°; its *oxime* at 143° and its *phenylhydrazone* at 139° with decomposition.

(2) Synthetically, from 1,3-diketones with suitable diazo-bodies: 4-**Methyl-5-acetylpyrazole,** b.p.$_{26}$ 161°, from its carboxylic acid (see below). 4-**Methyl-** and 4-**phenyl-3,5-diacetylpyrazoles,** m.p. 114° and 134°, from acetylacetone diazo-anhydride (Vol. I.) with acetyl- and benzoyl-acetone respectively (A. **325,** 183).

5. **Pyrazole Carboxylic Acids** are produced:

(1) By oxidizing alkyl pyrazoles with potassium permanganate. When several alkyl groups are present they are gradually changed to carboxyl.

(2) Pyrazole carboxylic esters are formed synthetically by the action of hydrazines upon the carboxylic esters of β-diketones or oxymethylene ketones:

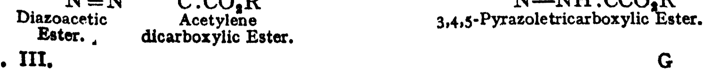


$$C_6H_5CO.CH_2.CO.CO_2R + NH_2.NHC_6H_5 > C_6H_5N—N=C(C_6H_5)—CH=C.CO_2R$$

Acetophenoneoxalic Ester. 1,3-Diphenyl-5-pyrazolecarboxylic Ester.

The γ-diketonic esters also, which result from the interaction of bromacetone, bromacetophenone, etc., with sodium acetoacetic ester, yield, by action of diazobenzene salts, with the splitting off of the acetyl group, phenylhydrazones of β-diketone carboxylic esters, which condense to pyrazole carboxylic esters (B. **26,** 1881).

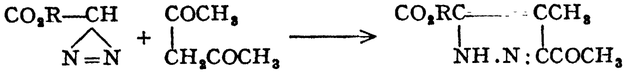
(3) Pyrazole carboxylic esters are formed by the addition of diazo-acetic esters to mono- and dicarboxylic acids of the acetylene series (B. **22,** 2165; A. **273,** 222):



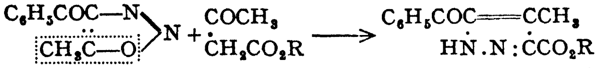
Diazoacetic Ester. Acetylene dicarboxylic Ester. 3,4,5-Pyrazoletricarboxylic Ester.

(*a*) Monohalogen substitution products of the acrylic and fumaric series and α,β-dihaloid substituted saturated acids—*e.g.*, α,β-dibromopropionic acid, dibromosuccinic acid, etc.—react with diazo-acetic ester.

(*b*) With β-diketones like acetylacetone, diazo-acetic ester reacts on heating with caustic soda with formation of such bodies as 4-**methyl-5-acetylpyrazole**-3-**carboxylic ester,** m.p. 198° (B. **36,** 1128):



(*c*) A similar reaction is shown by the diazo-anhydrides of β-diketones (compare furo[*ab*]diazols), which, on treatment with NaHO, split up intermediately into carboxylic acids and diazo-aliphatic bodies, and when treated with β-diketones or β-ketone carboxylic esters into diacylpyrazoles or acylpyrazolecarboxylic esters (A. **325,** 177):



Benzoyl-acetone-diazo-anhydride. 3,4-Benzoyl-methyl-pyrazole-5-carboxylic Acid.

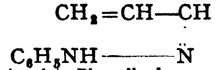
When the pyrazole carboxylic acids are heated carbon dioxide is evolved and pyrazole results. The carboxyl group in the 3-position is most easily split off. The next in order is that in the 5-position, while the COOH-group in the 4-position is most firmly combined (A. **278,** 273). There is no N-atom adjacent to it.

3- (or 5-) **Pyrazolecarboxylic Acid,** $C_3H_3N_2.COOH$, melting at 209° with decomposition, is obtained from 3-methylpyrazole, as well as from 3,5-pyrazolinedicarboxylic acid by the exit of carbon dioxide and H_2 (A. **273,** 237). 4-**Pyrazolecarboxylic Acid,** melting at 275°, is obtained from pyrazoletricarboxylic acid. 3,5-**Pyrazoledicarboxylic acid,** $C_3H_2N_2(COOH)_2$, melting at 289°, is made from methylpyrazole carboxylic acid, dimethylpyrazole (A. **279,** 218; B. **25,** R. 744), as well as from diazoacetic ester by means of dibromopropionic ester. 3,4,5-**Pyrazoletricarboxylic acid,** $C_3HN_2(COOH)_3$, melting at 233°, is prepared by methods 1 and 3.

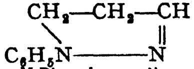
3-**Methyl**-5-**pyrazolecarboxylic acid,** $C_3H_2(CH_3)N_2.COOH$, melts at 236° (B. **25,** R. 744; A. **279,** 217). 3,5-**Dimethyl**-4-**pyrazolecarboxylic acid,** $C_3H(CH_3)_2N_2COOH$, melting with decomposition at 290°, is derived from acetyl- or ethidene-acetoacetic ester (A. **279,** 239). Two isomeric *C*-**Phenylpyrazoledicarboxylic acids,** $C_3(C_6H_5)HN_2(CO_2H)_2$, melting at 235° and 243°, have been obtained from diazo-acetic ester by means of phenylpropiolic and α-bromocinnamic acid (B. **27,** 3247). *N*-**Phenylpyrazolecarboxylic acids,** $C_3H_2N_2(C_6H_5)COOH$; the 3-*acid* melts at 146°, and the 5-*acid* melts at 183° (B. **24,** 1888). The 4-*acid* melts at 220°. It is obtained from *N*-phenylpyrazoletricarboxylic acid (B. **22,** 179). *N*-**Phenylmethylpyrazolecarboxylic acids,** $C_3H(CH_3)$-$N_2.C_6H_5(COOH)$. There are five known isomerides: (1) the 1,5,3-*acid,* melting at 136°, results from the action of diazobenzene chloride upon acetonylacetoacetic ester (method 2), as well as from acetoneoxalic ester and phenylhydrazine, together with (2) the 1,3,5-*acid,* melting at 190°, which is also produced by a peculiar rearrangement of phenylmethyloxpyridazone (A. **253,** 54; **295,** 305); (3) the 1,5,4-*acid,* melting at 166°, is obtained from hydroxymethyleneacetoacetic ester (A. **278,** 270; **295,** 311); (4) the 1,4,3-*acid,* melting at 134°, and (5) the 1,3,4-*acid,* melting at 192°, have been prepared by oxidation of phenyldimethylpyrazole (B. **25,** R. 943; **26,** R. 245). 1,5-**Diphenyl-3-pyrazolecarboxylic acid,** $C_3H(C_6H_5)N_2.C_6H_5(COOH)$, melting at 185°, is prepared from phenacylacetoacetic ester; **phenylpyrazoledicarboxylic acids** (compare A, **295,** 306). 1-**Phenylpyrazole**-3,4,5-**tricarboxylic Acid,** $C_3N_2.C_6H_5(COOH)_3$, melts at 184° (B. **22,** 172).

PYRAZOLINES.

Metallic sodium and alcohol reduce the pyrazoles, especially the *N*-phenylpyrazoles, to dihydropyrazoles or pyrazolines. The latter are also produced by rearrangement of the hydrazones of unsaturated aldehydes or ketones, in that the amine residue of the hydrazine adds itself to the unsaturated linkage:



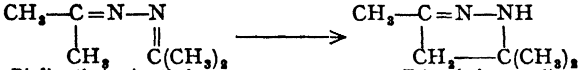
Acrolein Phenylhydrazone.



N-Phenylpyrazoline.

While this rearrangement proceeds with many hydrazones at lower temperatures, with others it is only completed when they are distilled. Frequently it occurs that the corresponding pyrazole is formed instead of the pyrazoline, or is produced along with the latter.

The ketazine of acetone, bisdimethylazimethylene, is capable of a rearrangement similar to the preceding. It is changed quite readily by maleïc acid into maleïnate of trimethylpyrazoline:



Bisdimethyl-azimethylene. 3,5,5-Trimethyl-pyrazoline.

Similar behaviour is shown by a series of homologous ketazines, and by ethylidenealdazine; *iso*butyraldazine is transposed by conc. HCl into 4,4-*dimethyl*-5-iso*propylpyrazoline* (J. pr. Ch. [2], **58,** 910; M. **20,** 84); but compare the transformation of bisdiethylazimethylene into dimethyldiethylpyrrole on heating with $ZnCl_2$ (B. **43,** 493).

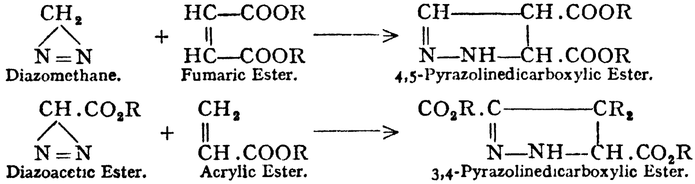
Behaviour.—The pyrazolines are feeble bases. They are, for the most part, only soluble in concentrated acids. They are less stable than the pyrazoles. Oxidizing agents convert them into very unstable dye substances, which are probably derived from bispyrazolines (B. **26,** 100; Knorr's pyrazoline reaction). When reduced they frequently yield trimethylenediamine derivatives; this is particularly true of the *N*-phenylpyrazolines.

Pyrazoline, $C_3H_6N_2 = \overline{CH_2—CH_2—CH = N—NH}$, is an oil boiling at 144°. It is formed from acrolein and hydrazine hydrate (B. **28,** 69; **29,** 774). 3,5,5-**Trimethylpyrazoline,** $C_3H_3(CH_3)_3N_2$, boiling at 66°–69° (20 mm.), is obtained from mesityl oxide and hydrazine, as well as from bis-dimethylazimethylene (see above); its *picrate* melts at 138° and its *maleïnate* at 127° (B. **27,** 770). 5-**Phenylpyrazoline,** $C_3H_5(C_6H_5)N_2$, is obtained from the hydrazone of cinnamic aldehyde (B. **27,** 788), as well as from its dicarboxylic acid (B. **26,** 261). *N*-**Phenylpyrazoline,** $C_3H_5N_2.C_6H_5$, melting at 52° and boiling at 274°, is converted by bromine into *N-phenyldibrompyrazoline,* $C_3H_3Br_2N_2.C_6H_5$, melting at 39°. 1,3,5-**Triphenyl-pyrazoline,** $C_3H_3(C_6H_5)_3N_2$, melting at 135°, is changed by bromine to *triphenyltribrompyrazoline,* $C_3(C_6H_5)_3Br_3N_2$, melting at 179°.

1-**Phenyl**-3,4,4-**trimethyl**-5-**hydroxypyrazoline,** $C_6H_5N.N{:}C(CH_3).C(CH_3)_2.CH(OH)$, m.p. 118°, from the corresponding pyrazolone by reduction, is converted by sulphuric acid into 1-phenyl-3,4,5-trimethyl pyrazole (B. **36,** 1275).

Pyrazoline ketones have been obtained by attaching diazo-methane to *αβ*-unsaturated ketones—*e.g.*, 4-**phenyl**-5-**acetylpyrazoline** from benzylidene acetone (C. 1906, II. 1130).

Pyrazolinecarboxylic acids are obtained from diazo-acetic ester or diazo-methane by means of olefine mono- and dicarboxylic acids or mono-haloid saturated acids. Diazo-methane acts similarly. Identical products are obtained with maleïc and fumaric acids, citr- and mesaconic acids, crotonic and *iso*crotonic acids (B. **33,** 3590):

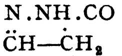


The pyrazolinecarboxylic acids show the rather remarkable peculiarity that when they are heated alone they break down into nitrogen and trimethylene carboxylic acids. Hydrazine is split off when they are heated with hydrochloric acid. Upon oxidation they become pyrazolecarboxylic acids; and when their silver salts are heated, pyrazoles are produced. Upon reduction they yield pyrazoline compounds in part (E. Buchner, A. **273,** 214).

Pyrazoline-3,5-**dicarboxylic acid,** $C_3H_4N_2(COOH)_2$, melts with decomposition at 242°. **Pyrazoline**-4,5-**dicarboxylic ester** (B. **27,** 1890), **pyrazoline**-3,4,5-**tricarboxylic methyl ester,** $C_3H_3N_2(COOCH_3)_3$, melting at 61°, and 3,4,5-**tricarboxypyrazolylacetic tetramethyl ester,** $C_3H_2N_2(CO_2CH_3)_3(CH_2.CO_2CH_3)$, melting at 105°, are obtained from diazo-acetic ester by means of fumaric and aconitic esters or from diazo-succinic ester with fumaric ester; pyrazolinetricarboxylic ester is also formed from diazo-acetic ester, and tricarboxypyrazolylacetic ester also from diazo-succinic ester on heating alone. In both cases a portion of the diazo-ester decomposes with formation of fumaric ester, and this then condenses with unchanged diazo-acetic ester or diazo-succinic ester (B. **34,** 345; **43,** 1095). 4-**Phenyl**-3,5-**pyrazoline dicarboxylic acid ester,** $C_3H_3(C_6H_5)N_2(COOR)_2$, from cinnamic ethyl ester and diazo-acetic methyl ester, or from cinnamic methyl ester and diazo-acetic ethyl ester, which give isomeric products, m.p. 76° and 107° respectively; the isomerism disappears on oxidation to the pyrazole derivatives (B. **35,** 31).

4-Phenyl-5-acetylpyrazoline-3,5-dicarboxylic ester, from benzylidene aceto-acetic ester and diazo-acetic ester, does not give a trimethylene derivative on heating, but an α-pyrone derivative (see B. **35,** 782).

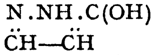
Pyrazolones.—Keto-pyrazolines or pyrazolones are, as already stated, desmotropic with the hydroxypyrazoles. According to the position of the CO-group, we distinguish 5- and 3-pyrazolones, among which are the oldest known derivatives of pyrazole:



$$\begin{array}{l} N.NH.CO \\ CH—CH_2 \end{array}$$

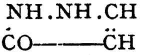
5-Pyrazolone.

or



$$\begin{array}{l} N.NH.C(OH) \\ CH—CH \end{array}$$

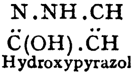
5-Hydroxypyrazole.



$$\begin{array}{l} NH.NH.CH \\ CO——CH \end{array}$$

3-Pyrazolone.

or



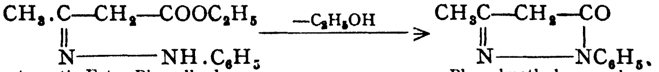
$$\begin{array}{l} N.NH.CH \\ C(OH).CH \end{array}$$

3-Hydroxypyrazole.

The keto-form is generally ascribed to the pyrazolones, though they behave in many reactions like hydroxy compounds. From the hydroxyl form may be derived the alkoxy- and acyl-oxy-pyrazoles formed by alkylation and acylation respectively.

The pyrazolones were discovered in 1883, and investigated by L. Knorr. Different pyrazolones have been previously discussed at the conclusion of the hydrazones of the β-ketonic acids, of which they are the inner anhydrides, and to which they sustain the same relation as the lactams bear to the corresponding amino-acids, hence the designation lactazams was suggested for the pyrazolones (I. 406).

They are produced (1) by the elimination of alcohol from the hydrazones of β-ketonic esters:



$$\begin{array}{l} CH_3.C—CH_2—COOC_2H_5 \\ \| \\ N———NH.C_6H_5 \end{array} \xrightarrow{-C_2H_5OH} \begin{array}{l} CH_3C—CH_2—CO \\ \|\qquad\qquad | \\ N———NC_6H_5 \end{array},$$

Acetoacetic Ester Phenylhydrazone. 1,3-Phenylmethyl-pyrazolone.

A number of these hydrazones, when acted upon with condensing agents which eliminate water—*e.g.*, hydrochloric acid, acetyl chloride, etc.—yield *alkoxypyrazoles*, which subsequently are converted by saponification of the alkoxy group into pyrazolones. Some of the phenylhydrazones of the β-ketonic esters, when treated with concentrated sulphuric acid, yield *indole* derivatives.

(2) From αβ-acetylene carboxylic esters and hydrazines (B. **27,** 783; C. 1906, II. 434).

(3) By the oxidation of the corresponding pyrazolidones.

Behaviour.—The pyrazolones, like the other pyrazole derivatives, are feeble bases (see, however, antipyrine). They also manifest the acid properties of the β-ketonic esters, and therefore yield unstable salts with bases just as they do with acids. They also have a series of reactions in common with the derivatives of β-ketonic acids. This is due to the reactivity of the CH_2-group standing between the two CO-groups; they condense to *benzylidene* derivatives with benzaldehyde, and with nitrous acid form iso*nitroso*- or *nitroso*-compounds, while with diazobenzene salts they yield more or less intensely coloured *azo*-compounds, etc. (B. **27,** 782; **28,** 625).

$POCl_3$ converts the pyrazolones into chlorinated pyrazoles. Heated with phosphorus tribromide under pressure, they immediately form pyrazoles (A. **352,** 322). On heating with P_2S_5 in xylene solution the pyrazolones are converted into thio-pyrazolones, while on heating the components to higher temperatures without solvents, pyrazoles are formed direct (see B. **40,** 3701; A. **361,** 251).

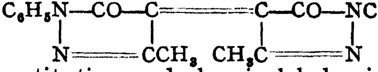
5-Pyrazolone, $\overline{\mathrm{CO.CH_2.CH:N.N}}\mathrm{H}$, melting at 164°, is best prepared from formylacetic ester (I. 401) and hydrazine, but is also produced from its carboxylic acids. It condenses with benzaldehyde, nitrous acid, and diazobenzene chloride to **4-Benzal-pyrazolone,** $\mathrm{(C_3H_2ON_2):CHC_6H_5}$, melting at 200°, **4-*iso*nitrosopyrazolone,** $\mathrm{(C_3H_2ON_2):NOH}$, melting with decomposition at 181°, and **4-pyrazolone-azobenzene,** $\mathrm{(C_3H_2ON_2):N.NHC_6H_5}$, melting at 196° (B. **29,** 249).

3-Methylpyrazolone, $\mathrm{C_3(CH_3)H_3ON_2}$, melting at 215°, is obtained by the action of hydrazine upon acetoacetic ester or dehydracetic ester (J. pr. Ch. [2], **39,** 132). **n-Phenyl-5-pyrazolone,** $\overline{\mathrm{CO.CH_2.CH:N.N}}\mathrm{.C_6H_5}$, melting at 118°, is obtained both from *N*-phenyl-3- and 4-pyrazolone carboxylic acids and from 1-phenyl-5-pyrazolidone. ***N*-Phenyl-3-pyrazolone,** $\overline{\mathrm{CH:CH.CO.NH.N}}\mathrm{C_6H_5}$, melting at 154°, results upon oxidizing 1-phenyl-3-pyrazolidone with ferric chloride, and by treating *N*-phenyl-pyrazoline successively with bromine and caustic potash, etc. (B. **28,** 35, 630; **29,** 519; J. pr. Ch. [2], **52,** 138).

***N*-Phenyl-3-methylpyrazolone,** $\overline{\mathrm{CO.CH_2.C(CH_3):N.N}}\mathrm{C_6H_5}$, melting at 127°, from acetoacetic ester, the β-chlorcrotonic esters (B. **29,** 1654), or tetrolic acid by means of phenylhydrazine, is that pyrazole derivative which is the best known, and, indeed, has been known for the longest time (A. **238,** 147). With benzaldehyde it yields the *benzylidene* compound, $\overline{\mathrm{CO.C(:CHC_6H_5)C(CH_3):N.N}}\mathrm{.C_6H_5}$, melting at 107°; the condensation products with hydroxybenzaldehydes are distinguished by strong coloration (B. **33,** 864). With $\mathrm{POCl_3}$, phenyl-methyl pyrazolone yields *N*-phenyl-3-methyl-5-chlorpyrazole, with $\mathrm{P_2S_5}$ in xylene ***N*-Phenyl-3-methyl-5-thiopyrazolone,** $\overline{\mathrm{CS.CH_2C(CH_3):N.N}}\mathrm{C_6H_5}$, m.p. 109° (A. **361,** 261). $\mathrm{N_2O_3}$ produces an iso*nitroso-derivative*, $\overline{\mathrm{CO.C(NOH).C(CH_3):N.N}}\mathrm{C_6H_5}$, m.p. 157°, which, on oxidation, yields **nitro-,** and on reduction **4-amino-*N*-phenyl-3-methyl-5-pyrazolone;** the latter is also obtained by the reduction of *N*-phenyl-3-methyl-5-hydroxypyrazoleazobenzene, obtained from phenylmethylpyrazolone and diazobenzene chloride (Constitution, see A. **378,** 218).

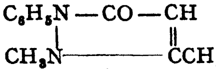
When the amino-derivative is oxidized it becomes *rubazonic acid*, $\mathrm{C_{20}H_{17}N_5O_2}$, melting at 181°. It is a red-coloured compound, which in its behaviour recalls the purpuric acid (I. 580) of the uric acid group. A large excess of the oxidant converts aminopyrazolone immediately into **1-phenyl-3-methylpyrazoledione,** $\overline{\mathrm{CO.CO.C(CH_3):N.N}}\mathrm{C_6H_5}$, the isatin of the pyrazole group, which, by reduction, yields the corresponding secondary alcohol: **4-hydroxy-1-phenyl-3-methyl-pyrazolone** (A. **293,** 50).

Ferric chloride oxidizes phenylmethylpyrazolone, with the union of two molecules, to *Pyrazole Blue*, which resembles indigo blue in constitution and chemical behaviour. Less energetic oxidants—*e.g.*, phenylhydrazine, etc.—produce *bis-phenylmethylpyrazolone*, which contains two atoms more of hydrogen. This can also be prepared from phenylmethylpyrazolone silver and iodine, as well as from the diphenylhydrazone of diacetosuccinic ester. The interaction of diazomethane and phenylmethylpyrazolone yields phenylmethylmethoxypyrazole (p. 80), and along with it, but in small quantity, the isomeric antipyrine (compare B. **28**, 1626).

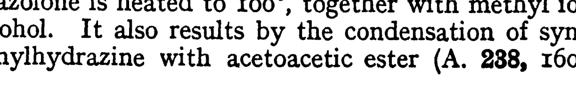

$$\begin{array}{l} C_6H_5N\text{—}CO\text{—}C\text{=====}C\text{—}CO\text{—}NC_6H_5, \\ N\text{=====}CCH_3 \quad CH_3C\text{=====}N \end{array}$$

***N*-Phenyl-4-methyl-5-pyrazolone,** $C_6H_5N.N{:}CH.CH(CH_3).CO$, m.p. 148°, from α-formylpropionic ester and phenylhydrazine, and, with the isomeric *N*-phenyl-4-methyl-3-pyrazolone, from bromomethacrylic ester, $CHBr{:}C(CH_3).COOR$, and phenylhydrazine (B. **38**, 3273). ***N*-Methyl-3-phenyl-5-pyrazolone,** $CH_3N.N{:}\,C(C_6H_5).CH_2.CO$, m.p. 207°, by methylation of 3-phenyl-5-pyrazolone, and by condensation of benzoylacetic ester with methylhydrazine, resembles in its reactions the technically useful phenylmethylpyrazolone (A. **352**, 152). 1,3-**Diphenyl-5-pyrazolone,** $C_6H_5N.N{:}\,C(C_6H_5).CH_2.CO$, m.p. 137°, from benzoylacetic ester and phenylhydrazine (A. **358**, 171).

Similarly to phenylmethylpyrazolone, it has been converted into 4-**keto**-1,3-**diphenyl**-5-**pyrazolone** and 4-**hydroxy**-1,3-**diphenyl**-5-**pyrazolone** (B. **36**, 1132).


$$\begin{array}{l} C_6H_5N\text{—}CO\text{—}CH \\ CH_3N\text{————}CCH_3 \end{array}$$

Antipyrine, 1,2,3-**Phenyldimethyl**-5-**pyrazolone,** melting at 114°, is obtained in the form of its hydriodide when phenylmethylpyrazolone is heated to 100°, together with methyl iodide and methyl alcohol. It also results by the condensation of symmetrical methylphenylhydrazine with acetoacetic ester (A. **238**, 160; B. **20**, R. 609):


$$\begin{array}{l} C_6H_5.NH \\ CH_3.NH \end{array} + \begin{array}{l} RO.CO.CH_3 \\ CO.CH_3 \end{array} = \begin{array}{l} C_6H_5N\text{—}CO\text{—}CH \\ CH_3N\text{———}CHCH_3 \end{array}.$$

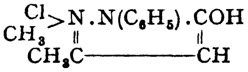
Homologues of antipyrine are formed, similarly to it, from phenylmethylpyrazolone: 2-**Benzyl**- and 2-**Ethyl**-1-**phenyl**-3-**methylpyrazolone,** *homoantipyrine*, melting at 119° and 73° respectively (J. pr. Ch. [2], **55**, 153; A. **293**, 3 footnote).

Antipyrine and its homologues are also produced by the heating of the halogen alkylates of 5-alkoxypyrazoles, and from the halogen alkylates of 5-chloro-pyrazoles with caustic alkalies; thus, the iodomethylate of 1,5-phenylchloropyrazole gives, with alkali, the lower homologue of antipyrine: 1-**Phenyl**-2-**methyl**-5-**pyrazolone,** m.p. 117°, also formed from 1-phenyl-5-pyrazolone with methyl iodide (A. **320**, 28). Isomers of antipyrine are 1,2-**dimethyl**-3-**phenyl**-5-**pyrazolone,** m.p. 108°, and 1-**phenyl**-2,4-**dimethyl**-5-**pyrazolone,** m.p. 125°, formed by methylating 1-methyl-3-phenyl- and 1-phenyl-4-methyl-5-pyrazolone respectively (A. **352,** 175; B. **38,** 3275). 1,2,3-**Trimethyl-5-pyrazolone** (see B. **43,** 2106.)

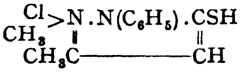
Antipyrine is a strong monacid base. It is very soluble in water and alcohol, and crystallizes from ether in shining leaflets.

It is highly prized in medicine as an antipyretic. Its *salicylate*, **salipyrine,** acts similarly to it. This is also true of the homologue **tolypyrine** or γ-tolyldimethylpyrazolone, etc.

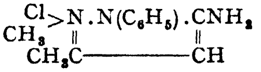
Transpositions of Antipyrine.—Antipyrine and its homologues give with $POCl_3$, **antipyrine chloride,** $C_{11}H_{12}N_2Cl_2$, m.p. 137°, which must be regarded as *1-phenyl-5-chloropyrazole-2-chloromethylate.* The Cl-atoms are mobile, especially the atom in the 5-position. Alkali regenerates antipyrine, alkali hydrosulphide or sodium thio-sulphate yields thiopyrine (see below), while NH_3 and amines give *imino-pyrines.* These compounds, like the antipyrines themselves, are all strongly basic, which, in contrast with the other pyrazole and pyrazolone derivatives, form very stable salts. The salts are therefore generally regarded as quaternary ammonium salts, according to the formula:



$$\begin{matrix} {}^{Cl}_{CH_3}{>}N.N(C_6H_5).COH \\ \| \qquad\qquad\qquad \| \\ CH_3C\text{————}CH \end{matrix}$$

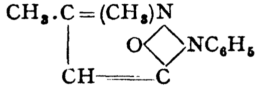


$$\begin{matrix} {}^{Cl}_{CH_3}{>}N.N(C_6H_5).CSH \\ \| \qquad\qquad\qquad \| \\ CH_3C\text{————}CH \end{matrix}$$

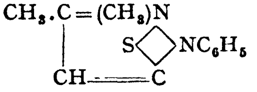


$$\begin{matrix} {}^{Cl}_{CH_3}{>}N.N(C_6H_5).CNH_2 \\ \| \qquad\qquad\qquad \| \\ CH_3C\text{————}CH \end{matrix}$$

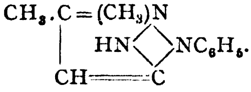
—*i.e.*, as halogen alkylates of 5-hydroxy-, 5-thiol-, and 5-amino-pyrazoles. The relations of these salts to their bases are, therefore determined by an addition or splitting off of acids in 2,5-position in the pyrazole nucleus, and A. Michaelis, therefore, also contemplates the following formulæ for the free bases (A. **320,** 1; **328,** 78; **331,** 197; **339,** 117; B. **36,** 3271):



Antipyrine.



Thiopyrine.



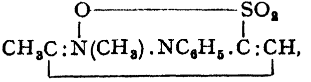
Iminopyrine.

From this point of view it is remarkable that the compounds obtained from antipyrine chloride with *p*-toluidine and from tolypyrine chloride with aniline are *not* identical (A. **339,** 130; compare also A. **352,** 154).

All 1,2-dialkylated pyrazolones behave like antipyrine and its homologues (A. **352,** 175; **354,** 55; B. **43,** 2106).

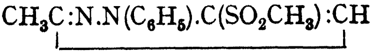
Thiopyrines.—**1-Phenyl-2-methyl-thiolpyrazole,** $C_3H_2SN_2(CH_3)(C_6H_5)$, m.p. 162°, from 1-phenyl-5-chloropyrazol-2-iodomethylate with KSH. **1-Phenyl-2,3-dimethyl-thiopyrazole,** *Thiopyrine,* $(CH_3)C_3HSN_2.(CH_3)(C_6H_5)$, m.p. 166°, from antipyrine chloride with KSH or $Na_2S_2O_3$ in aqueous solution, acts physiologically like antipyrine. **1-Phenyl-2-ethyl-thiolpyrazole,** m.p. 171°, **1-phenyl-2,3,4-trimethyl-thiolpyrazole,** m.p. 129°, etc. By repeated distillation or by heating their halogen alkylates, the thiopyrines are converted by the migration of the alkyl group from the N to the S-atom into pseudo-*thiopyrines* or *pyrazole alkyl sulphides*—*e.g.*, $\underbrace{CH_3C{:}N.N(C_6H_5).C(SCH_3){:}CH}$. Thiopyrines and *pseudo*-thiopyrines are distinguished by their behaviour on oxidation.

The former give trioxides, inner salts of sulphonic acids—*e.g.*,



$$CH_3C:N(CH_3).NC_6H_5.C:CH$$ (with O—SO$_2$ above)

the latter dioxides, sulphones,—*e.g.*,



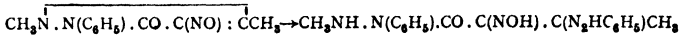
$$CH_3C:N.N(C_6H_5).C(SO_2CH_3):CH.$$

Iminopyrines.—1-**Phenyl-2,3-dimethyl-iminopyrazole,** *Iminopyrine,* $C_3H_2N_3(C_6H_5)(CH_3)_2$, from antipyrine chloride by heating with aqueous NH_3 or Am carbonate under pressure; its hydrochloride, on heating, splits up into CH_3Cl and 1,3-phenyl-methyl-5-amino-pyrazole, which unites again with methyl iodide to form iminopyrine hydriodide. **Anilinopyrine,** m.p. 59°, from antipyrine chloride and aniline, is transformed on heating its iodomethylate into 1,3-**phenyl-methyl-5-methyl-anilino-pyrazole. Phenyl-hydrazino-pyrine** (see B. **42,** 2765). Further iminopyrines, see B. **36,** 3279, etc.

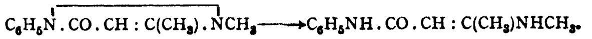
Like acids, alkyl iodides add themselves in the 2,5-position to antipyrine, forming methiodides of the 5-alkoxypyrazoles, but at higher temperatures antipyrine and methyl iodide produce 1-**phenyl-2,3,4-trimethyl-pyrazolone,** *methylantipyrine,* m.p. 82°, and on transposition 1-**phenyl-3,3,4-trimethyl-pyrazolone,** m.p. 56° (A. **293,** 1).

4-**Nitroso-antipyrine,** $(C_{11}H_{11}ON_2).NO$, from antipyrine with nitrous acid, on reduction with Zn and acetic acid, gives 4-**amino-antipyrine,** m.p. 109°, from which dyes are easily obtained in the form of diazo-compounds (A. **293,** 58). By methylation we obtain from amino-antipyrine **dimethyl-amino-antipyrine** $(C_{11}H_{11}ON_2)N(CH_3)_2$, m.p. 108°, the so-called *pyramidone* (C. 1897, I. 1006; 1900, II. 613). In the organism this is mostly changed into antipyryl urea and into rubazonic acid (B. **35,** 2891). 4-**Hydroxy-antipyrine,** m.p. 182°, is formed by methylating 4-hydroxy-1-phenyl-3-methyl-pyrazolone. It has a marked phenol character (A. **293,** 49).

Disintegration Products.—By heating with alc. potash antipyrine is broken up with formation of phenylmethylhydrazine (B. **39,** 3265). On heating (1) nitroso-antipyrine with phenylhydrazine, we obtain the *phenyl-hydrazone* of iso-*nitroso-aceto-acetic phenylmethylhydrazide* (A. **328,** 62). On heating antipyrine (2) with toluol and sodium in a current of CO_2 we obtain *β*-**methylamino-crotonic acid anilide** (B. **25,** 769):

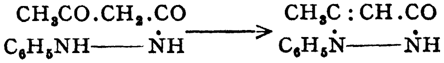
(1) 

$$CH_3N.N(C_6H_5).CO.C(NO):CCH_3 \rightarrow CH_3NH.N(C_6H_5).CO.C(NOH).C(N_2HC_6H_5)CH_3$$

(2) 

$$C_6H_5N.CO.CH:C(CH_3).NCH_3 \longrightarrow C_6H_5NH.CO.CH:C(CH_3)NHCH_3.$$

3-**Pyrazolones** are formed (1) by the action of PCl_3 upon a mixture of *β*-ketonic acid esters with acetyl or benzoyl phenylhydrazine, intermediate products being the phenylhydrazides of the *β*-ketonic acid (A. **338,** 269):



$$\begin{matrix} CH_3CO.CH_2.CO \\ C_6H_5NH\text{——}NH \end{matrix} \longrightarrow \begin{matrix} CH_3C:CH.CO \\ C_6H_5N\text{——}NH \end{matrix}$$

(2) By the action of phenylhydrazine upon *β*-hydroxyalkyl-acrylic ester (C. 1906, II. 434).

(3) By oxidation of the corresponding 3-pyrazolidones.

Behaviour.—The 3-pyrazolones resemble in their behaviour the 5-pyrazolones: like these, they possess both acid and basic characters.

$POCl_3$ converts them into 3-chloro-pyrazoles. With diazobenzene salts they form azo-dyes (A. **338,** 228), with N_2O_3 green 4-nitroso-compounds, converted by oxidation into strongly acid 4-nitro-pyrazolones, and by reduction into stable unoxidizable 4-amino-pyrazolones. On boiling with ferric chloride they give no dyes resembling pyrazole blue. The melting-points of the 3-pyrazolones are all higher than those of the corresponding 5-pyrazolones.

1-Phenyl-3-pyrazolone, $\overline{\mathrm{CH{:}CH.CO.NH.N}}\mathrm{C_6H_5}$, m.p. 155°, is formed from 1-phenyl-3-pyrazolone-4-carboxylic acid by heating; from 1-phenyl-3-pyrazolidone by oxidation with ferric chloride; and from *N*-phenyl-pyrazoline by successive treatment with bromine and potassium hydrate (B. **29,** 519; **40,** 1020).

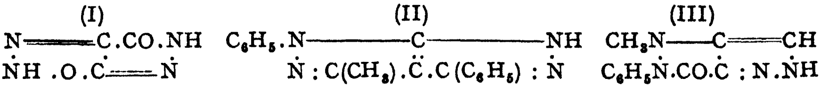
1,5-Diphenyl-3-pyrazolone, $\mathrm{C_6H_5}\overline{\mathrm{C{:}\,CH.CO.NH.N}}\mathrm{C_6H_5}$, m.p. 252°, by methods (1), (2), and (3); also by distillation of cinnamic phenyl hydrazide (B. **20,** 1107; A. **358,** 159).

1-Phenyl-5-methyl-3-pyrazolone, $\mathrm{CH_3}\overline{\mathrm{C{:}\,CH.CO.NH.N}}\mathrm{C_6H_5}$, m.p. 167°, by methods (1) and (3); on methylation it yields the *poisonous* **3-antipyrine** (isomeric with antipyrine), **1,2,5-phenyldimethylpyrazolone,** $\mathrm{CH_3}\overline{\mathrm{C{:}\,CH.CO.N(CH_3)N}}\mathrm{C_6H_5}$, m.p. 119° (B. **25,** R. 367; **28,** 629). This substance behaves chemically just like antipyrine. With $POCl_3$ it forms 3-antipyrine chloride, 1,5-*phenylmethyl*-3-*chloropyrazole-methochloride,* from which transformation with ammonia gives **3-iminopyrine,** with potassium sulphohydrate **3-thiopyrine,** and with potassium hydroselenide **3-selenopyrine** (B. **36,** 3290; A. **338,** 290). **1-Phenyl-4-methyl-3-pyrazolone,** $\overline{\mathrm{CH{:}\,C(CH_3).CO.NH.N}}\mathrm{C_6H_5}$, m.p. 210°, is formed beside 1-phenyl-4-methyl-5-pyrazolone from bromo-methacrylic acid ester and phenylhydrazine (B. **38,** 3273).

1,3-Phenyl-methyl-5-pyrazolone-4-aldehyde, $\mathrm{C_6H_5}\overline{\mathrm{N.N{:}\,C(CH_3).CH(CHO).C}}\mathrm{O}$, m.p. 174°, is formed from the condensation product of methylphenylpyrazolone with isatin-α-anil by fission with caustic soda (M. **31,** 73).

Pyrazolone Carboxylic Acids.—Their esters are obtained from the hydrazones of β-keto- or aldehydo-dicarboxylic esters. The acids readily break down into CO_2 and pyrazolones.

5-Pyrazolone-3-carboxylic acid, $\overline{\mathrm{CO.CH_2{-}C(COOH){=}N{-}N}}\mathrm{H}$, decomposes at 250°. Its *methyl ester* melts at 227°. It is formed from oxalo-acetic methyl ester, chlorofumaric ester (B. **29,** R. 860), or acetylene dicarboxylic ester with hydrazine (B. **25,** 3442; **26,** 1722). Nitrous acid converts it into an iso*nitroso*-compound, $\overline{\mathrm{CO{-}C(NOH).C(COOH){=}N{-}N}}\mathrm{H}$, melting at 201°, which yields the hydrazide of *hydrazipyrazolone carboxylic acid* when treated with hydrazine hydrate. The *anhydride* of this acid, decomposing at 126°, represents a symmetrical dicyclic nucleus (I.), which may also be viewed as the dilactazam of dioxosuccinic osazone (B. **26**, 2057). Compare the production of diphenylmethyldipyrazole (II.) (B. **36**, 523) and phenyl methyl pyrazo-pyrazolone (III.) (B. **41**, 3849).

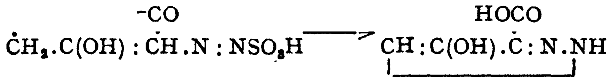


$$\begin{array}{lll} \text{(I)} & \text{(II)} & \text{(III)} \\ N{=\!=\!=}C.CO.NH & C_6H_5.N{-\!-\!-}C{-\!-\!-}NH & CH_3N{-\!-}C{=\!=}CH \\ NH.O.C{=\!=\!=}N & N:C(CH_3).C.C(C_6H_5):N & C_6H_5N.CO.C:N.NH \end{array}$$

5-Pyrazolone-4-carboxylic acid, $CO—CH(COOH)—CH=N.NH$. Its *ethyl ester* melts at 181°. It is formed, along with malonyl hydrazides, when hydrazine hydrate acts upon the ester of dicarboxyglutaconic acid, $(CO_2R)_2CH.CH:C(CO_2R)_2$, and when hydrazine and the ester of ethoxymethylenemalonic acid react (B. **28**, 1053). This acid splits off CO_2 quite easily and becomes pyrazolone (B. **28**, 988).

5-Pyrazolonyl-3-acetic ester, $(C_2H_5OCOCH_2)C_3H_3ON_2$, m.p. 190°, from acetonedicarboxylic ester with hydrazine (J. pr. Ch. [2], **64**, 334).

Isomeric with the 5-pyrazolone carboxylic acids is **4-hydroxypyrazole-3-carboxylic acid,** m.p. 205°, from diazo-tetrone sulphonic acid (I, 544) by heating with NaHO (A. **318**, 6):



$$\overset{-CO}{CH_2}.C(OH):CH.N:NSO_3H \longrightarrow CH:C(OH).\overset{HOCO}{C}:N.NH$$

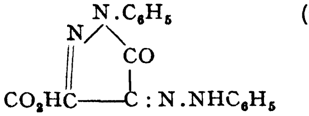
1-Phenyl-5-pyrazolone-4-carboxylic acid, $CO—CH(COOH)—CH=N—NC_6H_5$, melts at 93° with decomposition. Its *ethyl ester* melts at 118°. It is produced when phenylhydrazine acts upon the ester of dicarboxyl-glutaconic acid or the ester of ethoxymethylenemalonic ester (I. 561). The isomeric **1-Phenyl-5-pyrazolone-3-carboxylic Acid,** melting at 181°, is produced in the form of its ester from oxalo-acetic ester and phenylhydrazine. Both phenylpyrazolone carboxylic acids yield the same phenylpyrazolone (B. **28**, 41).

1-Phenyl-3-pyrazolone-4-carboxylic acid, $CH:C(COOH).CO.NH.NC_6H_5$, m.p. 216° with dec., is obtained in the form of its ester by the action of PCl_3 upon a mixture of ethoxy-methylene-malonic ester and acetylphenylhydrazine (B. **40**, 1020). **1-Phenyl-4-hydroxypyrazole-3-carboxylic acid,** m.p. 154°, from the phenylhydrazone of γ-brom-aceto-acetic ester, splits off CO_2 and yields 1-phenyl-4-hydroxypyrazole.

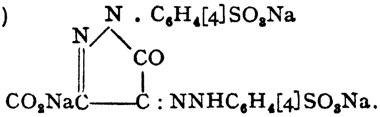
Pyrazolone Azo-Dyes.—The power of combining with diazonium salts mentioned in the case of the phenylmethylpyrazoles is a general property of the 5-pyrazolones not substituted in the 4-position. The pyrazolone azo-dyes can not only be obtained by direct coupling of the pyrazolones with diazonium salts, but also by first preparing benzeneazo-β-ketonic acid ester from β-ketonic acid esters and diazonium salts (compare benzeneazoacetoacetic ester), and subsequently converting this into pyrazolone azo-compounds by the action of hydrazines (B. **31**, 467). The pyrazolone dyes must be regarded as real azo-derivatives of 5-hydroxy-pyrazoles (A. **378,** 218). Some of them are important dyestuffs (compare C. 1901, I. 486; 1902, II. 918, etc.; also G. Cohn, *Die Pyrazolon Farbstoffe,* Stuttgart, 1910). Among them is particularly the valuable yellow dye, *tartrazine.*

The osazones of the diketosuccinic acid esters readily yield the ester of **1-phenyl-pyrazole-4,5-dione-3-carboxylic acid phenylhydrazone** (1). This has a red colour. It melts at 154°. It is the parent substance of the valuable yellow dye **tartrazine** (2), the chief constituent of which is the trisodium salt of **tartrazinic acid** or **1-*p*-sulphophenylpyrazole-4,5-dione-3-carboxylic acid 4-*p*-sulphophenylhydrazone :**

(1)



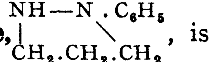
(2)

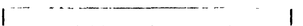


The latter acid can also be obtained from 1,*p*-sulphophenyl-3-pyrazolone carboxylic acid and from the diazide of sulphanilic acid, which fully demonstrates its constitution (A. **294,** 219).

PYRAZOLIDINES.

The derivatives of *tetrahydropyrazole* or *pyrazolidine* pass easily, as a general thing, into pyrazoline compounds; therefore they possess reducing properties. The simplest pyrazolidine is not yet known.

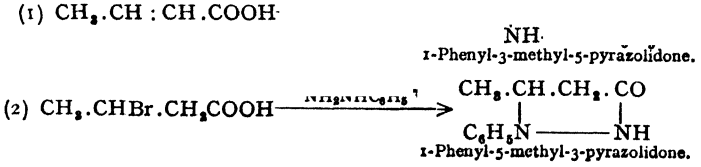
***N*-Phenylpyrazolidine,**  $\begin{matrix}NH—N.C_6H_5\\ |\qquad\quad\diagdown\\ CH_2.CH_2.CH_2\end{matrix}$, is an oil. It boils at 160° (20 mm.). It is formed when sodium phenylhydrazine acts upon trimethylene bromide (B. **26,** R. 402). The oxygen of the air oxidizes it to phenylpyrazoline. Alkali and methyl iodide convert it into

1 - Phenyl - 2 - methylpyrazolidine,  $\overline{CH_2—CH_2—CH_2.N(CH_3)N}C_6H_5$, boiling at 175°–180° (90 mm.). The reduction of the corresponding pyrazolidone produces **1-phenyl-3-methylpyrazolidine** (B. **26,** 107). 1,3,5-**Triphenyl-2-methylpyrazolidine,** melting at 110°, results in the reduction of triphenylpyrazole iodmethylate with sodium and alcohol.

Pyrazolidinecarboxylic acids have been obtained by the reduction of pyrazolinecarboxylic acids (B. **26,** R. 282).

Keto-derivatives of the pyrazolidines :

(1) **Pyrazolidones** result from the interaction of hydrazines and β-haloid fatty acids or α,β-olefine carboxylic acids. If phenylhydrazine be employed, it is possible for the reaction to pursue a double course, according as the secondary or tertiary group of the hydrazine is attacked by the carboxyl group of the acid:


(1) CH$_3$.CH : CH.COOH
NH
1-Phenyl-3-methyl-5-pyrazolidone.
(2) CH$_3$.CHBr.CH$_2$COOH
NH$_2$NHC$_6$H$_5$
CH$_3$.CH.CH$_2$.CO
C$_6$H$_5$N
NH
1-Phenyl-5-methyl-3-pyrazolidone.

The resulting isomerides are distinguished by the fact that the 1-phenyl-5-pyrazolidones have only *basic* properties, whereas the 1-phenyl-3-pyrazolidones also possess *acid* properties. On oxidation the pyrazolidones readily become pyrazolones, and when reduced with sodium and alcohol they are converted in part into pyrazolidines (see below).

Pyrazolidone, $CH_2.CH_2.CO.NH.NH$, boiling at 133°–135°, is obtained from acrylic acid and hydrazine. It is a base. When oxidized it yields pyrazolone (J. pr. Ch. [2]; **51,** 73). **1-Phenyl-5-pyrazolidone,** $CO.CH_2.CH_2.NH.N.C_6H_5$, melting at 78°, is derived from *β*-haloid propionic acids by means of sodium formylphenylhydrazine, or from acrylic acid with phenylhydrazine in toluene solution (B. **28,** 26). It is only basic, and when oxidized it becomes 1-phenyl-5-pyrazolone, melting at 118°.

The isomeric **1-Phenyl-3-pyrazolidone,** $CH_2.CH_2.CO.NH.N.C_6H_5$, melting at 119°–121°, and obtained from *β*-haloid propionic acid with free phenylhydrazine, as well as from *unsym.* *β*-phenylhydrazinopropionic ester (B. **24,** R. 234), possesses acid properties also, and when oxidized becomes 1-phenyl-3-pyrazolone, melting at 154°; its *N-acetyl* derivatives melt at 67° (B. **29,** 517).

1-Phenyl-3-methyl-5-pyrazolidone, melting at 84° and boiling at 321°, is derived from crotonic acid and phenylhydrazine or from symmetrical *β*-phenylhydrazinobutyric acid (B. **27,** R. 687). It is a base. It readily changes to 1,3-phenylmethylpyrazolone. When methylated it yields 1,2,3-**phenyldimethylpyrazolidone,** *hydroantipyrine,* melting at 146°. It cannot be converted by oxidation into antipyrine (B. **26,** 103).

1-Phenyl-5-methyl-3-pyrazolidone, m.p. 128°, from *unsym.* *β*-phenyl-5-hydrazino-butyric acid, has also acid properties; oxidation produces 1,5-**phenyl-methyl-3-pyrazolone.** 1,5,5,3- and 1,3,3,5-**phenyldimethyl pyrazolidone,** m.p. 110° and 75°, are produced by chlor*iso*valerianic acid, and from dimethylacrylic acid with phenyl-hydrazine; the 1,5,5,3- acid is split up by boiling with baryta-water to *β*-benzeneazo-*iso*valeric acid (C. 1897, II. 1100; A. **292,** 284). 1,5-**Diphenyl-4-hydroxy-3-pyrazolidone,** m.p. 173° (see C. 1905, I. 173).

(2) *Diketopyrazolidines* are the cyclic hydrazides of the *malonic acids:* 3,5-**Diketopyrazolidine,** *Malonylhydrazine,* $CO.CH_2.CO.NH.NH$, is an oil. It is formed from malonic ester and hydrazine (B. **28,** R. 159.)

1-**Phenyl**-3,5-**diketopyrazolidine,** *Malonyl-phenylhydrazine,* melting at 192°, is obtained from the phenylhydrazide of malonic ester acid (B. **25,** 1506); from malonic acid ester, phenylhydrazine, and sodium ethylate (B. **39,** 2282); or by the action of PCl_3 upon a mixture of malonic acid and acetylphenylhydrazine (B. **40,** 3568). It is probably a phenyl-hydroxy-pyrazolone. With $POCl_3$ under gentle heat it yields 1-**phenyl**-3-**chloropyrazolone,** m.p. 144°, and at 130° phenyldichloropyrazole (B. **31,** 3003). 1-**Phenyl**-4,4-**dimethyl**-3,5-**diketopyrazolidine,** m.p. 176,° from dimethylmalonic acid, acetylphenylhydrazine, and PCl_3 (B. **41,** 3865).

2. INDAZOLES.

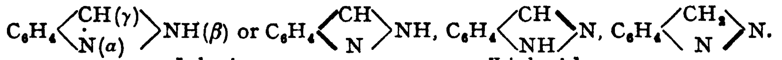
Just as the benzopyrroles or indoles correspond to the pyrroles, so do the benzopyrazoles or indazoles correspond to the pyrazoles.

There are two isomeric series of *N*-alkylic indazoles. The one series is produced by the action of alkyl iodides upon indazole or its homologues. The second series, called isindazoles, result synthetically from ortho-substituted α-alkylphenylhydrazines, and therefore have the alkyl residue attached to the N-atom adjacent to the benzene nucleus; consequently, in the isomeric *N*-alkyl indazoles the alkyl residue must be joined to the second (β-) N-atom.

These two groups of benzopyrazoles are therefore derivable from Formulæ I. and II. (below); the fundamental bodies may be desmotropic.

A third desmotropic formula (III.) may be constructed from *indolenine*, the desmotropic indole formula; from this Formula III. the indiazone oximes, and probably the diazoindazoles (see p. 96), are derivable:

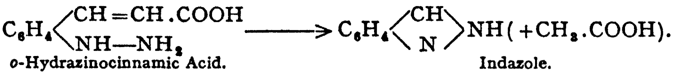
I. II. III.



$$C_6H_4\langle{}^{CH(\gamma)}_{N(\alpha)}\rangle NH(\beta) \text{ or } C_6H_4\langle{}^{CH}_{N}\rangle NH,\quad C_6H_4\langle{}^{CH}_{NH}\rangle N,\quad C_6H_4\langle{}^{CH_2}_{N}\rangle N.$$

Indazole. [Isindazole].

Indazoles result (1) upon heating the *o*-hydrazinocinnamic acids (E. Fischer, A. **227**, 303):

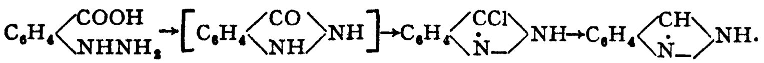


$$C_6H_4\langle{}^{CH=CH.COOH}_{NH-NH_2} \longrightarrow C_6H_4\langle{}^{CH}_{N}\rangle NH(+CH_3.COOH).$$

o-Hydrazinocinnamic Acid. Indazole.

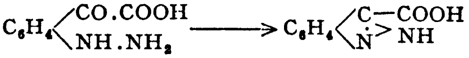
It is singular that a lactam-like anhydride of the hydrazinocinnamic acid is not formed in this reaction. It would contain a seven-membered ring. Indazylacetic acid is produced by the moderated oxidation of *o*-hydrazinocinnamic acid.

(2) Hydrazinobenzoic acid, heated with $POCl_3$ under pressure, gives γ-chlorindazole, which is reduced to indazole by zinc and HCl (B. **35**, 2315):



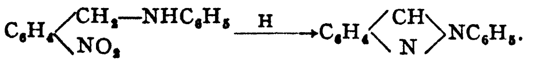
$$C_6H_4\langle{}^{COOH}_{NHNH_2} \rightarrow \left[C_6H_4\langle{}^{CO}_{NH}\rangle NH\right] \rightarrow C_6H_4\langle{}^{CCl}_{N}\rangle NH \rightarrow C_6H_4\langle{}^{CH}_{N}\rangle NH.$$

(3) From the elimination of water from *o*-hydrazino-acetophenone or *o*-hydrazino-phenylglyoxylic acids:



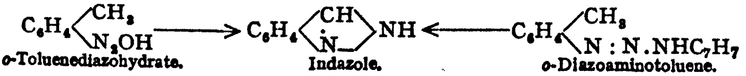
$$C_6H_4\langle{}^{CO.COOH}_{NH.NH_2} \longrightarrow C_6H_4\langle{}^{C-COOH}_{N} > NH$$

(4) *N*-Phenylindazoles are formed in the reduction of *o*-nitrobenzylanilines (B. **24**, 961; **27**, 2899):



$$C_6H_4\langle{}^{CH_2-NHC_6H_5}_{NO_2} \xrightarrow{H} C_6H_4\langle{}^{CH}_{N}\rangle NC_6H_5.$$

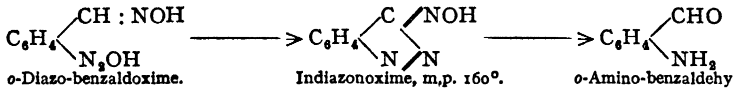
(5*a*) Further, indazoles are formed by the careful decomposition of diazobenzene derivatives methylated in the ortho-position (B. **26**, 2349; A. **305**, 289):



$$C_6H_4\langle{}^{CH_3}_{N_2OH} \longrightarrow C_6H_4\langle{}^{CH}_{N}\rangle NH \longleftarrow C_6H_4\langle{}^{CH_3}_{N:N.NHC_7H_7}$$

o-Toluenediazohydrate. Indazole. *o*-Diazoaminotoluene.

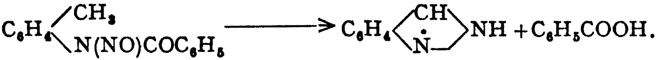
By this method numerous indazoles substituted in the benzene nucleus have been obtained. The diazo-hydrate from *o*-toluidine, boiled in acid solution, gives only *o*-cresol, in neutral solution some indazole and γ-tolueneazo-indazole; substituted benzeneazo-indazoles are formed chiefly on the decomposition of *o*-methyl diazobenzenes in strongly alkaline solution, the indazoles formed coupling with undecomposed diazo-solution. A complete reaction with formation of indazole is only shown by the diazo-bodies from nitrated *o*-methyl anilines, which yield indazoles on simply boiling with mineral acids, or by treating with glacial acetic acid (B. **37**, 2556). On diazotizing *o*-amino benzaldoximes, the so-called ***indiazone oximes*** are formed, which easily isomerize in water or alkali to *o*-azido-benzaldehydes (B. **34**, 1309):



$$C_6H_4\Big\langle\begin{matrix}CH:NOH\\N_2OH\end{matrix} \longrightarrow C_6H_4\Big\langle\begin{matrix}C\diagup NOH\\ \diagdown\\ N\diagup N\end{matrix} \longrightarrow C_6H_4\Big\langle\begin{matrix}CHO\\NH_2\end{matrix}$$

o-Diazo-benzaldoxime. Indiazonoxime, m.p. 160°. *o*-Amino-benzaldehyde.

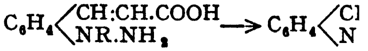
(5*b*) The smoothest reaction is that in which indazoles are formed from the nitroso-compounds of acylated *o*-methylanilines by heating in benzene solution (B. **41**, 660):



$$C_6H_4\Big\langle\begin{matrix}CH_3\\N(NO)COC_6H_5\end{matrix} \longrightarrow C_6H_4\Big\langle\begin{matrix}CH\\N\end{matrix}\Big\rangle NH + C_6H_5COOH.$$

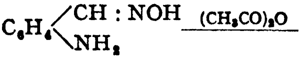
Isindazoles are formed:

(1) From *o*,α-alkylhydrazinocinnamic acids or *o*,α-alkylhydrazinoacetophenones:



$$C_6H_4\Big\langle\begin{matrix}CH:CH.COOH\\NR.NH_2\end{matrix} \longrightarrow C_6H_4\Big\langle\begin{matrix}C\\N\end{matrix}$$

(2) From *o*-amino-aldoximes or ketoximes by glacial acetic acid and acetic anhydride (B. **26**, 1903; **29**, 1261):

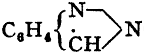


$$C_6H_4\Big\langle\begin{matrix}CH:NOH\\NH_2\end{matrix} \xrightarrow{(CH_3CO)_2O}$$

(3) From the phenylhydrazones of *o*,*p*-dinitrophenyl-glyoxylic esters we obtain **nitro-α-phenylindazole-γ-carboxylic ester** (B. **22**, 319):

Properties.—Indazoles are mostly crystalline, feebly basic, bodies, the *Bz*-nitro-indazoles also form salts with metals (B. **37**, 2570). They are not easily oxidized; β-phenylindazole is split up to form azobenzene carboxylic acid by chromic acid. Hydro-products are formed with difficulty. The free imino-group is easily alkylated and acylated; with diazo compounds, indazoles and the *Bz*-substituted indazoles couple up to form benzene-azo-indazoles; and with benzaldehyde to form benzylidene bisindazole, $C_6H_5CH(C_7H_5N_2)_2$. The isindazoles have a general resemblance to the indazoles. The substituents of the pyrazole ring are usually designated by Py-α, β-, γ-, and those of the benzene ring by Bz-1-, 2-, 3-, 4-, starting with the nitrogen attached to the benzene ring.

Indazole, $C_7H_6N_2$, m.p. 146°, b.p. 270°, is formed from its carboxylic acid, from *o*-hydrazinocinnamic acid, from chlorindazole, from benzoyl-*o*-tolyl-nitrosamine, from *o*-diazotoluene chloride with NaHO, and by diazotising *o*-amino-benzaldehyde (B. **25,** 1754). β-**Hydroxy-indazole,**



$C_6H_4\left\{\begin{matrix}N- \\ \dot{C}H\end{matrix}\right\rangle NOH$, m.p. 139°, a strong acid, from *o*-triazo-benzaldoxime by boiling with NaHO, is reduced by Zn and HCl to indazole (B. **35,** 1891).

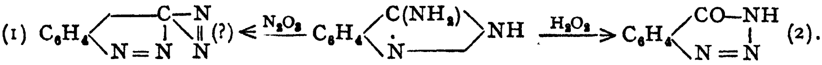
β-**Benzyl-indazole,** $C_7H_5N_2.CH_2.C_6H_5$, m.p. 73°, from γ-chloro-β-benzyl-indazole by reduction (B. **35,** 2318). With $NaNO_2$ indazole gives nitrosoindazole, $C_7H_5N_2.NO$, m.p. 74°.

Bz-1-**Methyl-,** -3-**Methyl-,** and -1,3-**Dimethylindazole,** m.p. 138°, 115°, and 134°, are formed from the xylidines and from mesidine by method (5*a*) and (5*b*) (A. **305,** 308, 363; B. **41,** 666). γ-**Methyl indazole,** $C_7H_6(CH_3)N_2$, m.p. 113°, b.p. 281°, from *o*-hydrazinoacetophenone, gives with acetyl chloride β-**acetyl-γ-methylindazole,** $C_7H_4(CH_3)N_2.COCH_3$, m.p. 72° (B. **24,** 2380), and with methyl iodide β,γ-**dimethylindazole,** $C_7H_5(CH_3)N_2.CH_3$, melting at 80°. β-**Phenyl-indazole,** $C_7H_5N_2.C_6H_5$, melting at 84° and boiling at 345°, is formed from nitrobenzyl aniline. Methyl iodide unites with it to an *iodo-methylate,* melting at 188°, and is oxidized by chromic acid to azobenzene-carboxylic acid (B. **24,** 3058; **27,** 48). γ-**Phenyl-indazole,** melting at 108° or 116°, is produced by the reduction of *o*-diazo-benzophenone. When sodium sulphite is used for this purpose, there first results an oxygen-containing body, $C_{13}H_{10}N_2O$, melting at 126°, which probably is a β-**hydroxy-γ-phenyl-indazole,** that upon further reduction becomes phenylindazole (B. **29,** 1265). Of the twelve possible nitromethyl indazoles, eleven have been prepared from the nitroxylidines; also several **dinitro-methyl-, nitro-dimethyl-,** and **dinitro-dimethyl indazoles.** By the reduction of these nitro-indazoles *Bz*-**amino-indazoles** have been prepared (B. **37,** 2556).

γ-**Azo-, Amino-,** and **Diazo-indazole.**—γ-Azo-derivatives of the indazoles are produced by the action of alkaline diazo-solutions upon the indazoles. They therefore result, beside the indazoles, in the decomposition of *o*-methylated diazonium salts with alkali: **Indazole-γ-azobenzene,** $C_7H_5N_2(N:NC_6H_5)$, orange needles, m.p. 191°; **indazole-γ-azo-toluene,** m.p. 211°, from *o*-diazo-toluene; **dimethyl-indazole-γ-azomesitylene,** m.p. 258°, from diazomesidine. **Nitro-indazole-γ-azo-nitro-methylbenzene** (see B. **37,** 2579).

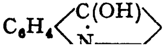
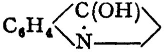
By reduction these azo-compounds are broken up into anilines and γ-amino-indazoles. γ-**Amino-indazole,** $C_7H_5N_2(NH_2)$, m.p. 154°, is also formed by diazotizing and then reducing *o*-amino-benzonitrile, transposing the intermediate *o*-cyano-phenylhydrazine (B. **42,** 3716) *Bz*-3-**methyl-** and -1,3-**dimethyl-γ-amino-indazole,** m.p. 191° and 151° respectively.

With HNO_2 the amino-indazoles yield fairly stable diazo-hydrates, $C_7H_5N_2(N_2OH)$, etc., which split off H_2O and form peculiar inner anhydrides of even greater stability, the so-called "*indazole triazolenes*" (1). **Indazole triazolene,** *diazo-indazole,* $C_7H_4N_4$, yellow needles, m.p. 106°; they easily couple with phenols and naphthols to form hydroxy-azo-dyes. With the halogen hydrides they yield γ-halogen indazoles. By oxidizing the amino-indazoles with H_2O_2, bichromate, etc., in acid solution, we obtain, with secondary splitting of the ring, benzazimides (2) (A. **305**, 289; B. **32**, 1773, 1797· **35**, 892):



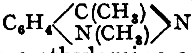
In alkaline solution the amino-indazoles are oxidized to azo-indazoles by atmospheric oxygen: **Azo-indazole,** $(C_7H_5N_2)N:N(C_7H_5N_2)$, deep red needles, m.p. 229° (B. **39**, 4276).

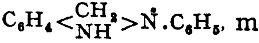
γ-**Chlorindazole,** $C_7H_5ClN_2$, m.p. 148°, from diazo-indazole with HCl, or from o-hydrazinobenzoic acid on heating with $POCl_3$ under pressure; the Cl-atom is very firmly bound. Nitrosation and acetylation produce β-**nitroso-** and **acetyl-chlorindazole** respectively, m.p. 90° and 67°; methyl iodide and alkali give β-**methyl-chlorindazole,** b.p. 269°. β-**Benzyl**-γ-**chlorindazole,** m.p. 47°, from *sym.* benzylhydrazino-o-benzoic lactazam with $POCl_3$ (B. **34**, 795; **35**, 2315).

γ-**Hydroxy**-β-**phenylindazole,**  $C_6H_4\langle{}^{C(OH)}_{N}\rangle NC_6H_5$, m.p. 218°, is formed from o-benzeneazo-benzaldehyde-acetal, $C_6H_5N:NC_6H_4CH(OCH_3)_2$, by saponifying with dilute SO_4H_2 (C. 1907, I. 1575). γ-**Hydroxy**-β-**phenylindazolecarboxylic acid,**  $C_6H_4\langle{}^{C(OH)}_{N}\rangle NC_6H_4COOH$, m.p. 228°, is obtained in the form of its lactone, m.p. 295°, under the action of $POCl_3$ upon o-hydrazobenzoic acid (C. 1906, II. 611); and by boiling oo′-azoxybenzaldehyde with glacial acetic acid (B. **42**, 1706).

γ-**Indazolecarboxylic acid,** $C_7H_5N_2.COOH$, melting with decomposition at 259°, is derived from o-hydrazino-phenyl-glyoxylic acid, which is prepared from isatinic acid, thus completing the transition from the indole to the indazole group (B. **26**, 217). When the acid is heated it breaks down into indazole and carbon dioxide.

γ-**Indazylacetic acid,** $C_7H_5N_2.CH_2.COOH$, results from the moderated oxidation of o-hydrazocinnamic acid. It melts at 169°, and decomposes into carbon dioxide and γ-methylindazole.

α,γ-**Dimethylisindazole,**  $C_6H_4\langle{}^{C(CH_3)}_{N(CH_3)}\rangle N$, melting at 36°, is made by the reduction of nitroso-o-ethylamino-acetophenone. **Py**-α-**Acetyl isindazole,** $C_7H_5N_2.COCH_3$, **Py**-α-γ-**Acetylmethyl-** and α,γ-**Acetyl phenylisindazole,** melting at 103° and 185°, are formed by method (2) from o-amino-benzaldoxime, -acetophenone-oxime, and -benzophenone-oxime. Alkalies again resolve them into these oximes (B. **29**, 1255). α-**Ethyl**-γ-**isindazylacetic acid,** $C_7H_4N_2(C_2H_5)(CH_2.COOH)$, melting at 132°, is obtained from nitroso-o-ethylamino-cinnamic acid. See above for α-**phenylisindazole** and **nitro**-α,γ-**phenylisindazolecarboxylic acid.**

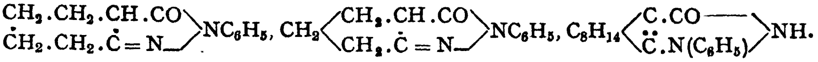
Hydro-isindazole Derivatives.— β-**Phenyldihydroindazole,**  $C_6H_4<{}^{CH_2}_{NH}>N.C_6H_5$, melting at 138°, is produced by the reduction of phenylindazole with sodium and alcohol.

Bz-**Nitro**-α-**phenyldihydroindazole**-γ-**carboxylic acid,** melting at 235°, is formed in the reduction of nitrophenylindazolecarboxylic acid (A. **264**, 149).

There are also some products arising from the combination of quinones with diazomethane, probably benzo- and naphtho-dihydro-pyrazoles. Benzoquinone and diazo-methane yield a very stable substance, probably represented by $\mathrm{N}\langle\begin{smallmatrix}\mathrm{CH}\\ \mathrm{NH}\end{smallmatrix}\rangle\mathrm{C_6H_4O_2}\langle\begin{smallmatrix}\mathrm{CH}\\ \mathrm{NH}\end{smallmatrix}\rangle\mathrm{N}$. α-Naphthoquinone and naphthazarin give $\mathrm{C_{10}H_6O_2}\left\{\begin{smallmatrix}\mathrm{CH}\\ \mathrm{NH}\end{smallmatrix}\right\rangle\mathrm{N}$ and $\mathrm{C_{10}H_4(OH)_2O_2}\left\{\begin{smallmatrix}\mathrm{CH}\\ \mathrm{NH}\end{smallmatrix}\right\rangle\mathrm{N}$ respectively. The triacetyl derivative of the latter body gives on oxidation with HNO_3 *pyrazole*-4,5-*dicarboxylic acid*. Similar products are obtained from diazo-methane with trinitro-benzene and picric acid (B. **32,** 2292; **33,** 627).

Indazolone, or *Benzo-pyrazolone*, is the inner anhydride or lactazam of *o*-hydrazinobenzoic acid, $\mathrm{C_6H_4}<\begin{smallmatrix}\mathrm{CO}\\ \mathrm{NH}\end{smallmatrix}>\mathrm{NH}$ (A. **213,** 333).

Nitro-β-phenylindazolone is formed from the ester of nitrophenyl-hydrazidobenzoic acid (B. **30,** 1100). We must include here the dicyclic pyrazolone derivatives obtained from cycloketone-β-carboxylic esters with phenylhydrazine—*e.g.*:

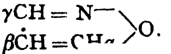


$$\begin{matrix}\mathrm{CH_2.CH_2.CH.CO}\\ \dot{\mathrm{C}}\mathrm{H_2.CH_2.}\dot{\mathrm{C}}\mathrm{=N}\end{matrix}\Big\rangle\mathrm{NC_6H_5},\quad \mathrm{CH_2}\Big\langle\begin{matrix}\mathrm{CH_2.CH.CO}\\ \mathrm{CH_2.}\dot{\mathrm{C}}\mathrm{=N}\end{matrix}\Big\rangle\mathrm{NC_6H_5},\quad \mathrm{C_8H_{14}}\Big\langle\begin{matrix}\mathrm{C.CO}\text{———}\\ \ddot{\mathrm{C}}\mathrm{.N(C_6H_5)}\end{matrix}\Big\rangle\mathrm{NH}.$$

Similarly, camphor oxalic ester with phenylhydrazine yields phenyl campho-pyrazole carboxylic ester (compare B. **32,** 1987; C. 1897, II. 123; A. **317,** 27).

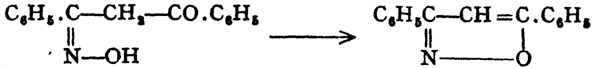
Benzodipyrazolones are **Hexahydro-benzo-dipyrazolone,** $\mathrm{NH}\langle\begin{smallmatrix}\mathrm{CO}\\ \mathrm{N}\end{smallmatrix}\rangle\mathrm{C_6H_4}\langle\begin{smallmatrix}\mathrm{CO}\\ \mathrm{N}\end{smallmatrix}\rangle\mathrm{NH}$, m.p. 257°, from succinylsuccinic acid ester and hydrazine and **benzo-bis-*N*-phenyl-pyrazolone, dicarboxylic acid,** $\mathrm{(COOH)_2C_6}\left(\begin{smallmatrix}\mathrm{—CO}\\ \mathrm{—NH}\end{smallmatrix}\rangle\mathrm{NC_6H_5}\right)_2$, from hydro-quinone tetra-carboxylic ester with phenylhydrazine (Ann. Ch. J. **12,** 379).

3. ISOXAZOLE- OR FURO[a]MONAZOLE GROUP.



$$\begin{matrix}\gamma\mathrm{CH=N}\text{—}\\ \beta\dot{\mathrm{C}}\mathrm{H=CH}\alpha\end{matrix}\Big\rangle\mathrm{O}.$$

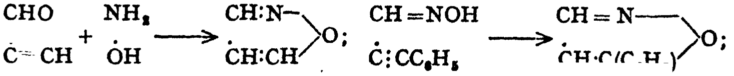
Isoxazole is the azole of furan: *Furo*[a]*monazole*, corresponding to pyrazole or pyrro[*a*]monazole. The isoxazoles resemble the pyrazoles both in structure and modes of preparation. As the latter result from the hydrazones of the β-diketo-compounds, so the isoxazoles are formed (1) from the monoximes of β-diketones and β-ketone aldehydes or hydroxymethylene ketone by rejection of water (Claisen, B. **24,** 3906):



$$\begin{array}{l}\mathrm{C_6H_5.C{—}CH_2{—}CO.C_6H_5}\\ \quad\ \,\|\\ \quad\ \mathrm{N{—}OH}\end{array}\xrightarrow{\qquad}\begin{array}{l}\mathrm{C_6H_5C{—}CH{=}C.C_6H_5}\\ \qquad\ \|\qquad\qquad |\\ \qquad\mathrm{N}\text{————}\mathrm{O}\end{array}$$

Benzoylacetophenone Monoxime. α,γ-Diphenylisoxazole.

(2) Isoxazole and α-alkylisoxazoles are formed from α-acetylene aldehydes with hydroxylamine (B. **36,** 3665; **44,** 1161; C. 1904, II. 187):

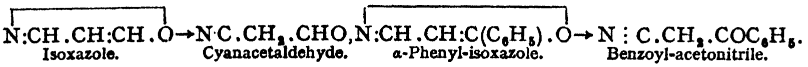


$$\begin{matrix}\mathrm{CHO}\\ \dot{\mathrm{C}}\mathrm{\equiv CH}\end{matrix}+\begin{matrix}\mathrm{NH_2}\\ \dot{\mathrm{O}}\mathrm{H}\end{matrix}\xrightarrow{\qquad}\begin{matrix}\mathrm{CH{:}N}\text{—}\\ \dot{\mathrm{C}}\mathrm{H{:}CH}\end{matrix}\Big\rangle\mathrm{O};\quad \begin{matrix}\mathrm{CH=NOH}\\ \dot{\mathrm{C}}\mathrm{{:}CC_6H_5}\end{matrix}\xrightarrow{\qquad}\begin{matrix}\mathrm{CH=N}\text{——}\\ \dot{\mathrm{C}}\mathrm{H{\cdot}C(C_6H_5)}\end{matrix}\Big\rangle\mathrm{O};$$

Similarly, α-acetylene ketones with hydroxylamine yield α,γ-disubstituted isoxazoles (C. 1904, I. 43; II. 710).

On the formation of isoxazoles from nitroparaffins by the action of alkali, see B. **24,** R. 767.

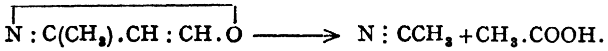
Properties.—The isoxazoles, like the pyrazoles, are feeble bases, while the α,γ-disubstituted isoxazoles are very stable towards alkalies, the isoxazoles with free γ-position are transposed into β-keto-nitriles by alcoholic alkali even cold:



$$N{:}CH.CH{:}CH.O \rightarrow N{:}C.CH_2.CHO, \quad N{:}CH.CH{:}C(C_6H_5).O \rightarrow N : C.CH_2.COC_6H_5.$$

Isoxazole. Cyanacetaldehyde. α-Phenyl-isoxazole. Benzoyl-acetonitrile.

Isoxazole with bound γ-position but free α-position are broken up on heating with alcoholic potash into carboxylic acids and nitriles (B. **36,** 3672):



$$N : C(CH_3).CH : CH.O \longrightarrow N : CCH_3 + CH_3.COOH.$$

On ring splitting by reduction, see B. **24,** 3912.

Isoxazole, C_3H_3NO, b.p. 95°, D_{14} 1·0843, a mobile liquid with odour resembling pyridine, gives with $PtCl_4$ and with $CdCl_2$ crystalline compounds (B. **36,** 3665). α- and γ-**Methyl-isoxazoles,** $(CH_3)C_3H_2NO$, b.p. 122° and 118° respectively, are formed together from hydroxymethylene-acetone and NH_2OH; α-methylisoxazole also from tetrolaldehyde or its acetal with hydroxylamine (B. **44,** 1161).

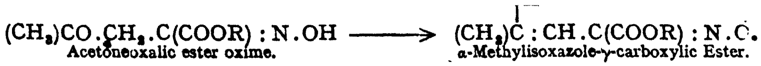
α,β,γ-**Trimethylisoxazole,** m.p. 3·5°, b.p. 248°, from methylacetyl acetone oxime, and from nitro-ethane with alkali (J. Ch. Soc., 1891, 410). α-**Phenylisoxazole,** m.p. 23°, b.p. 247°, results from phenyl propiol aldoxime with cold NaHO, and is transposed by sodium ethylate solution into phenacyl cyanide; it is also formed, beside the isomeric γ-phenylisoxazole, from hydroxymethylene acetophenone with NH_2OH (B. **36,** 3673).

α,γ-**Phenylmethylisoxazole,** m.p. 68°, $b.p._{19}$ 125°, from benzoyl acetone or phenylacetylacetylene (C. 1904, I. 43). On heating with alcoholic ammonia it gives 3,5-phenylmethylpyrazole.

β-**Nitro-isoxazole,** $(NO_2)C_3H_2NO$, m.p. 46° to 47°, from nitromalonic dialdehyde (Vol. I.) with 1 mol. hydroxylamine, is split up by water to cyano-nitro-acetaldehyde (C. 1903, I. 958). γ-**Phenyl-β-nitroisoxazole,** $(C_6H_5)(NO_2)C_3HNO$, m.p. 116°, is formed from cinnamic aldehyde with nitrous gases. It is split up by alc. potash, forming benzonitrile and nitro-acetic ester. Reduced with Al amalgam it gives γ-**phenyl-β-amino-isoxazole,** $b.p._{12}$ 179° (A. **328,** 245).

γ-**Nitro-α,γ-diphenyl-β-nitro-isoxazole,** m.p. 199°, from benzal acetophenone with N_2O_3, etc. (A. **328,** 224).

Isoxazole Carboxylic Acids.—Their esters are formed from the oximes of ketoneoxalic esters:



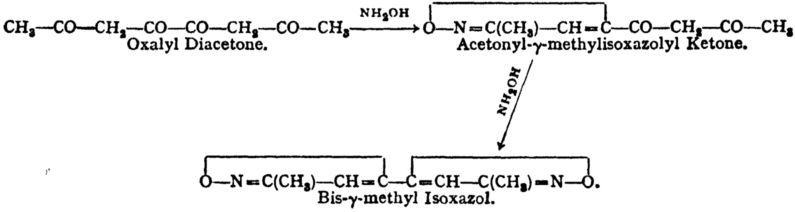
$$(CH_3)CO.CH_2.C(COOR) : N.OH \longrightarrow (CH_3)C : CH.C(COOR) : N.O.$$

Acetoneoxalic ester oxime. α-Methylisoxazole-γ-carboxylic Ester.

α-**Methylisoxazole-γ-carboxylic acid,** $CH_3(C_3HNO)COOH$, m.p. 176°, and γ-**methylisoxazole-α-carboxylic acid,** m.p. 211°; their esters are formed together from acetoneoxalic ester and NH_2OH. The free acids cannot be split up into CO_2 and isoxazoles, but decompose completely on heating (B. **24,** 3908).

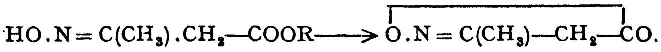
α-Methylisoxazole-β-γ-dicarboxylic acid, $CH_3(CNO)(COOH)_2$, m.p. 183° with dec., is obtained in the form of diethyl ester, m.p. 57°, by the action of fuming nitric acid upon mono- or diaceto-succinic ester (B. **42,** 1869).

Bis-isoxazoles result from the interaction of oxalyldiketones and hydroxylamine:


CH₃—CO—CH₂—CO—CO—CH₂—CO—CH₃
Oxalyl Diacetone.
NH₂OH
O—N=C(CH₃)—CH=C—CO—CH₂—CO—CH₃
Acetonyl-γ-methylisoxazolyl Ketone.
NH₂OH
O—N=C(CH₃)—CH=C—C=CH—C(CH₃)=N—O.
Bis-γ-methyl Isoxazol.

Acetonyl-γ-methylisoxazolyl ketone appears as an intermediate product. It can also be made by the condensation of γ-methylisoxazole-α-carboxylic ester with acetone (B. **24,** 3910).

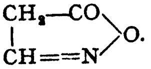
Isoxazolones.—These are keto-derivatives of the hypothetical dihydro-isoxazole or isoxazoline. They correspond to the pyrazolones or lactazams, consequently can also be designated as *lactazones* or *lactoximes*. They result when the oximes of the β-ketonic esters lose alcohol (B. **24,** 140; **30,** 1159; A. **296,** 33):



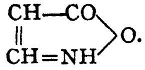
$$HO.N=C(CH_3).CH_2—COOR \longrightarrow O.N=C(CH_3)—CH_2—CO.$$

A series of compounds, obtained from glyoxal, methylglyoxal, phenylglyoxal, etc. (also their oximes), by the action of hydroxylamine hydrochloride, can also be considered as the oximes of isoxazolone derivatives (compare B. **30,** 1287).

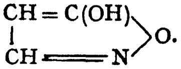
The isoxazolones, similarly to the pyrazolones, can be variously formulated:

I. 

$$\begin{matrix} CH_2—CO \\ | \\ CH==N \end{matrix}\Big\rangle O.$$

II. 

$$\begin{matrix} CH—CO \\ \| \\ CH=NH \end{matrix}\Big\rangle O.$$

III. 

$$\begin{matrix} CH=C(OH) \\ | \\ CH===N \end{matrix}\Big\rangle O.$$

The isoxazolones have a very pronounced acid nature. They decompose the alkaline earth carbonates in the cold, and form salts not only with metals, but also with ammonia and primary amines. The constitution of these salts varies. Ethers result from the action of alkyl iodides upon the silver salts. Methylamine is liberated when phenyl-isoxazolone-methyl ether is distilled with caustic potash. The methyl group is therefore probably linked to nitrogen, and the compound is derived from Formula II. (A. **296,** 37).

γ-Methylisoxazolone, $C_4H_5NO_2$, melting at 170°, is made from the oxime of aceto-acetic ester. *Barium salt,* $(C_8H_7O_3N_2)_2Ba + 1\frac{1}{2}H_2O$. The *ammonium salt,* $(C_8H_7O_3H_2)NH_4$; *methyl ester,* $(C_8H_7O_3N_2)CH_3$ (A. **296,** 46). When the oxime of aceto-acetic ester is condensed in the presence of diazobenzene salts, the *phenylhydrazone* of *γ-methyl-β-ketoisoxazoline,* $(C_4H_3NO_2):NNHC_6H_5$, melting at 192°, results. The condensation of the same oxime in the presence of ketones or aldehydes gives rise to *iso***propylidene** and **benzylidenemethylisoxazolones,**

$(C_4H_3NO_2):C(CH_3)_2$, melting at 121°, and $(C_4H_3NO_2):CH.C_6H_5$, melting at 141° (B. **30**, 1337).

*iso***Nitroso-methyl-isoxazolone** (compare B. **28**, 2093; **30**, 1342). The simplest isoxazolone is still unknown, but is probably represented by a descendant, the so-called *meta-fulminuric acid,* iso*nitroso-oxazolone oxime,* $O.N:CH.C(:NOH).C:NOH$, which deflagrates at 106°. It is formed by voluntary polymerization of fulminic acids. On heating with water, or more quickly by the action of alkalies, it is transposed into cyan*iso*nitroso-acethydroxamic acid, $CN.C(:NOH).C(:NOH)\text{-}OH$ (B. **42**, 1346). **Amino-*iso*nitroso-isoxazolone,** m.p. 160° with dec. (see A. **367**, 83).

γ-Phenylisoxazolone, $C_9H_7NO_2$, melts at 152°. *Silver salt,* $C_9H_6NO_2Ag$; *aniline salt,* $C_9H_7NO_2.NH_2C_6H_5$, melts at 111°. *Methyl ester,* $C_9H_6NO_2.CH_3$, melts at 78°. The action of benzoyl chloride and alkali produces two *benzoyl esters* of phenylisoxazolones, insoluble in alkalies, melting at 161° and 115° (B. **30**, 1614). **β,γ-Dimethylisoxazolone,** melts at 124°. **γ,β-Methylethylisoxazolone** melts at 50° (A. **296**, 56). **γ,β-Methylbenzylisoxazolone** melts at 106° (B. **30**, 1161).

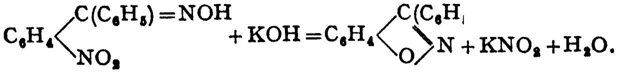
γ-Phenyl-α-imino-isoxazoline, $\overline{O\text{—}N=C(C_6H_5)\text{—}CH\text{—}C}:(NH)$, melting at 111°, results from cyanacetophenone, $C_6H_5.CO.CH_2.CN$, or benzoacetonitrile and hydroxylamine (B. **27**, 1095; Jr. pr. Ch. [2], **47**, 124). **γ-Phenyl-α-benzoyl-β-isoxazolone,** melting at 175°, is obtained from αδ-diphenylbutane-αβδ-trione-γ-ol (p. 381) and hydroxylamine (B. **25**, 3468; compare B. **30**, 1290):

$$\underset{\text{αδ-diphenylbutane-αβδ-trione-γ-ol.}}{C_6H_5CO\text{—}CO\text{—}CH(OH)\text{—}CO.C_6H_5} + NH_2OH \rightarrow \underset{\text{Phenylbenzoyl β-isoxazolone.}}{\overline{O\text{—}N=C(C_6H_5)\text{—}CO\text{—}CH}.CO.C_6H_5}.$$

α-Isoxazolone-β-carboxylic ester, $\overline{O.N:CH.CH(CO_2C_2H_5)CO}$, is formed from ethoxy-methylenemalonic acid ester, and from dicarboxy-glutaconic ester with hydroxylamine. On heating its silver salt with methyl iodide it yields an N-methyl derivative, $\overline{O.N(CH_3).CH:C(CO_2C_2H_5)CO}$ (A. **297**, 81; B. **30**, 1480).

4. INDOXAZENE OR BENZISOXAZOLE GROUP.

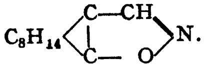
Indoxazenes or benzisoxazoles are formed from the oximes of *o*-halogen- or *o*-nitro-benzophenones with alkali, and from *o*-aminobenzophenone with HNO_2 (B. **25**, 1498; **26**, 1657. See method (3) of forming isindazoles):



$$C_6H_4\left\langle\begin{matrix}C(C_6H_5)=NOH\\ NO_2\end{matrix}\right. + KOH = C_6H_4\left\langle\begin{matrix}C(C_6H_5)\\ O\end{matrix}\right\rangle N + KNO_2 + H_2O.$$

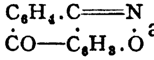
The simplest indoxazene, which should arise from bromo- or *o*-nitrobenzaldoxime, appears not to be stable, as it immediately rearranges itself into salicylnitrile (compare isoxazoles; B. **26**, 1253). *Anthranil* can be regarded as an isomeric benzo-β-γ-isoxazole, according to formula $C_6H_4\left\langle\begin{matrix}CH\\ N\end{matrix}\right\rangle O$ or $C_6H_4\left\langle\begin{matrix}CH\\ N\end{matrix}\right\rangle O$ (compare also benzisooxazolone, $C_6H_4<^{CO}_{NH}>O$). **Phenylindoxazene,** $C_{13}H_9NO_2$, melting at 84° and boiling at 331°–336°, yields a dinitro-derivative with fuming nitric acid. When it is reduced with sodium and alcohol it decomposes into *a*-*o*-hydroxyphenylbenzylamine, $C_6H_4<^{CH(C_6H_5)NH_2}_{OH}$, while HI and phosphorus change it to *o*-benzoylphenol (B. **28,** R. 604; **29,** R. 350). Consult B. **27,** 1452; **28,** 1872, R. 290, for other indoxazene derivatives.

Compare C. 1897, II. 123, for campho-isoxazole,



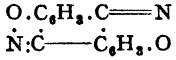
$C_8H_{14}<^{C—CH}_{C—O}>N$.

Anthroisoxazole,



$\begin{array}{l} C_6H_4.C{=\!=}N \\ CO—C_6H_3.O \end{array}$

and **Anthradiisoxazole,**

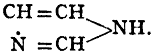


$\begin{array}{l} O.C_6H_3.C{=\!=}N \\ N{:}C—C_6H_3.O \end{array}$

(see B. **43,** 3251).

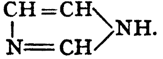
The following groups of [b]-*monazoles* of *pyrrole, thiophen,* and *furan,* the glyoxalines, thiazoles, and oxazoles, can also be regarded as cyclic amidines, imido-ethers, and thio-imido-ethers of carboxylic acids, as shown by their formations. By reduction these compounds cannot in general be converted into hydrated bases. They are usually split up or remain unchanged (see **29,** 2381).

5. GLYOXALINES OR PYRRO-[b]-MONAZOLES:



$\begin{array}{l} CH{=}CH \\ N{=}CH \end{array}>NH.$

Glyoxaline is isomeric with pyrazole; like the latter, it may be viewed as a nitrogen substitution product of pyrrole, and hence be designated as *pyrro*-[b]-*monazole,*

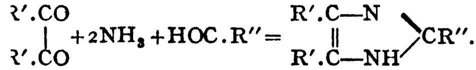


$\begin{array}{l} CH{=}CH \\ N{=}CH \end{array}>NH.$

Again, the glyoxalines may be considered cyclic amidines, just as is done with ring-homologous pyrimidines.

History.—Debus (1856) discovered glyoxaline as a reaction product of ammonia and glyoxal. Radziszewski (1882) explained this reaction and applied it to other diketones. Those peculiar bases—the *oxalines*—prepared by Wallach (1876) from the dialkyl-oximide chlorides, were found later to be glyoxalines. Japp (1882), cognizant of the relations existing between the lophines and glyoxalines, made them the basis for the constitution formula of the glyoxalines accepted to-day almost universally. Indeed, it has been established by the more recent syntheses of Wohl and Markwaldt, and of Bamberger.

Glyoxalines result (1) from the condensation of glyoxal and other *o*-diketo-compounds with ammonia and aldehydes (B. **15,** 2706):

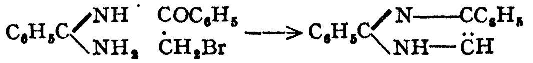


$$\begin{array}{l} R'.CO \\ R'.CO \end{array} + 2NH_3 + HOC.R'' = \begin{array}{l} R'.C—N \\ R'.C—NH \end{array}>CR''.$$

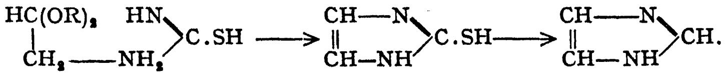
Glyoxaline is formed when ammonia acts upon glyoxal. This is dependent upon a partial decomposition of the glyoxal into formic aldehyde and formic acid.

Allied to this reaction is the production of glyoxalines from 1,2-diketones and amines of the formula $RCH_2.NH_2$. Benzil and benzylamine yield *triphenyl*-N-*benzyl-glyoxaline,* while with ethylamine the product is *diphenyl-2-methyl*-N-*ethyl glyoxaline* (B. **28,** R. 302).

(2) From carboxylic acid amidines with α-halogen ketones or α-ketone alcohols (B. **34**, 637; **29**, R. 673; compare oxazoles and thiazoles):

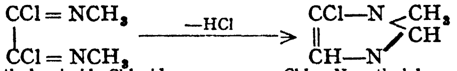


The thioureas from aminoacetals and aminoketones yield, by inner condensation, mercaptans of glyoxalines, which, upon oxidation, part with H_2SO_4 and become glyoxalines (B. **22**, 1353; **25**, 2354; **26**, 2204):



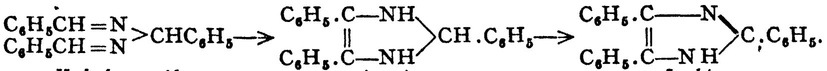
Triphenylglyoxaline is similarly produced from benzoin and benzamidine (B. **29**, R. 673).

(3) The alkylimide chlorides of oxalic acid, by peculiar reactions, change to chloro-substitution products of the glyoxalines and yield the latter upon reduction (A. **214**, 278):



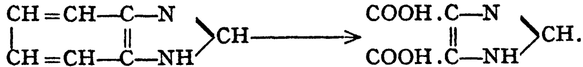
Dimethyl-oximide Chloride. α-Chlor-*N*-methylglyoxaline.

(4) Hydrobenzamide and similarly constituted aromatic compounds, when heated, rearrange themselves to dihydroglyoxalines, which readily change to glyoxalines:



Hydrobenzamide. Amarine, Triphenyldihydro-glyoxaline. Lophine, Triphenyl-glyoxaline.

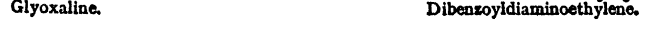
(5) A very interesting formation, theoretically speaking, of glyoxaline carboxylic acid consists in oxidizing benzoglyoxaline or benziminazole with potassium permanganate (A. **273**, 339):



Benziminazole. Iminazoledicarboxylic Acid.

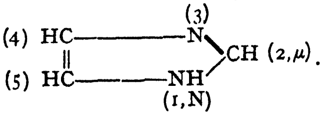
(6) Certain iminazoles have been obtained from the corresponding oxazoles on heating them with ammonia (B. **29**, 2098).

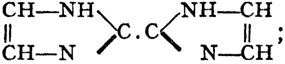
Properties.—The glyoxalines are stronger bases than the isomeric pyrazoles. Their imine hydrogen can be replaced by metals, especially silver, and also by alkyl residues through the agency of alkyl iodides. The tertiary bases take up alkyl iodides very energetically. The *N*-alkylglyoxalines are rearranged on heating, the alkyl residue migrating to the (μ) C-atom, occupying the position between the two N-members. Acyl-groups are only introduced with difficulty, and are easily split off. Benzoyl chloride and sodium hydroxide occasion, rather strangely, even at 0°, decomposition into carboxylic acids and dibenzoyldiamines:



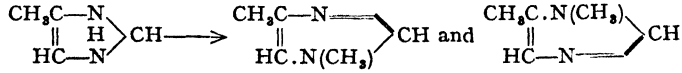
Glyoxaline. Dibenzoyldiaminoethylene.

The glyoxalines are very stable toward reducing agents, and are but slightly altered by oxidants. Hydrogen peroxide produces oxamines.

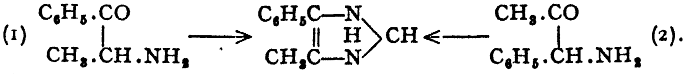
The position of the substituents in glyoxalin is indicated in the following manner: . The μ-alkyl derivatives are also termed *glyoxal ethyline, glyoxal propyline,* etc., according to the aldehyde used in the synthesis, as they are chiefly made by the action of ammonia and aldehydes upon glyoxal.

Glyoxaline, Iminazole, $C_3H_4N_2$, melting at 90° and boiling at 263°, is formed, together with *glycosine* (probably *bisglyoxaline,*  ; compare B. **20,** R. 431), from glyoxal and ammonia, better with addition of formic aldehyde (A. **277,** 336); also from glyoxaline-2-mercaptan, as well as from its carboxylic acid. It is soluble in alcohol, ether, and water. Its solutions, containing alkali, phosphoresce on exposure to the air (compare lophine). It forms salts with all acids excepting carbonic acid. Silver nitrate precipitates *silver glyoxaline,* $C_3H_3N_2Ag$, and methyl iodide forms *N*-**Methylglyoxaline,** $C_3H_3N_2CH_3$, melting at − 6° and boiling at 199°, with sp. gr. 1·0363. This can also be obtained from dimethyloximide chloride according to method of formation 3 (above). *N*-**Phenylglyoxaline,** $C_3H_3N_2.C_6H_5$, melting at 13° and boiling at 276°, is formed by method 2 from its mercaptan.

4- (or 5-) **Methylglyoxaline,** $C_3H_3(CH_3)N_2$, m.p. 56°, b.p. 263°, from its mercaptan (B. **26,** 2204); physiological importance attaches to the formation of 4-methylglyoxalines by the action of zinc hydrate and ammonia upon grape-sugar and other hexoses and pentoses (B. **38,** 1166; **40,** 799). The methylation of methylglyoxalines with dimethyl sulphate and alkali gives rise simultaneously to 1,4- and 1,5-**dimethylglyoxaline,** b.p. 199° and 224°:



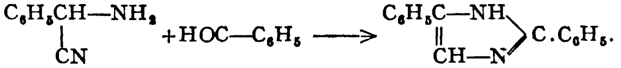
The methylglyoxaline therefore behaves during methylation like a mixture of 4- and 5-methylglyoxaline (C. 1910, II. 1480). 2,4,5-**Trimethyl-glyoxaline,** $C_3(CH_3)_3N_2H$, m.p. 183°, b.p. 271°, from diacetyl, NH_3 and aldehyde. 4-**Phenyl-glyoxaline,** m.p. 129°, from phenylglyoxal, NH_3 and formaldehyde. With NH_3 alone, phenyl-glyoxal gives, among other compounds, 2,4-phenyl-benzoyl-glyoxaline, m.p. 280° (B. **38,** 1531). 4,5-**Methyl-phenyl-glyoxaline,** m.p. 185°, has been prepared from methyl-phenyl-imidazolyl-mercaptan by oxidation with NO_3H, and the same methyl-phenyl-glyoxaline is formed whether one starts with α-amino-propiophenone (1) or by the isomeric α-phenyl-α-amino-acetone (2):



This proves the equivalence of the 4- and 5-position in glyoxaline (B. **41,** 1926); compare also μ-**methyl-toliminazole, 3-methyl-pyrazole,** and Vol. I. under virtual tautomerism.

2,4-**Diphenylglyoxaline,** m.p. 193°, from benzamidine and phenacylbromide. 4,5-**Diphenyl-glyoxaline,** m.p. 227°, from benzil, formaldehyde and NH_3, besides benzilam, benzilimide, and imabenzil (B. **35,** 4136; **38,** 1536).

2,5-**Diphenylglyoxaline,** $C_3H(C_6H_5)_2N_2H$, melting at 162°, is produced on heating 2,5-diphenyloxazole to 300° with alcoholic ammonia; also by the condensation of phenyl-α-aminoacetonitrile and benzaldehyde by means of hydrochloric acid (compare method of forming oxazoles; B. **29,** 2103):



2,4,5-**Triphenylglyoxaline, Lophine,** melting at 275°, is produced:

(1) From benzil, benzaldehyde, and ammonia.

(2) When hydrobenzamide is distilled or amarine oxidized.

(3) By the reduction of triphenylcyanidine or triphenyl tricyanogen; ammonia is eliminated.

(4) From benzamidin and benzoin (B. **29,** R. 673).

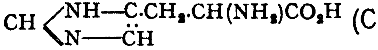
Lophin (from λόφος, tuft of feathers, alluding to its tufted crystalline form) exhibits in marked degree the property of phosphorescing when shaken with alcoholic potash; it is then decomposed into ammonia and benzoic acid. Like the glyoxalines, it does not form an acetate.

The halogen derivatives of the glyoxalines result from substitution; also by the splitting off of hydrogen chloride from the dialkyloximide chlorides. **Tribromo-glyoxaline,** $C_3Br_3N_2H$, melting at 214°, is formed from glyoxaline and bromine. **Chloro-*N*-methylglyoxaline,** $C_3H_2ClN_2.CH_3$, boiling at 205°, and **Chloro-1,2-dimethylglyoxaline,** $C_3HCl(CH_3)N_2.CH_3$, boiling at 218°, are obtained from dimethyl- and diethyloximide chloride.

Nitro-derivatives of the glyoxalines are obtained by the action of nitro-sulphuric acid or fuming nitric acid upon glyoxaline. The nitro-group probably takes up the 4- or 5-position. The nitro-glyoxaline, with a free imino-group, dissolves in alkalies with a yellow colour. **Nitro-4-methyl-glyoxaline,** $C_3H_2(NO_2)N_2.CH_3$, m.p. 248°; **Nitro-2,4-dimethyl-glyoxaline,** m.p. 252°; **Nitro-1,4-dimethyl-glyoxaline,** m.p. 161° (B. **42,** 761).

Sulph-hydro-derivatives are formed from acetalyl- or acetonyl-thioureas and similar substances by condensation; **2-Iminazolyl-mercaptan,** $C_3H_3(SH)N_2$, m.p. 222° with dec., gives with methyl-iodide **iminazolyl-2-methyl-sulphide,** $C_3H_3(SCH_3)N_2$, m.p. 139° (B. **25,** 2359). 4,5-**Diphenyl-glyoxaline-2-mercaptan,** $C_3(C_6H_5)_2HN_2(SH)$, is formed from benzoin with thiourea (A. **284,** 8; B. **31,** 1220). 4- (or 5-) **Amino-methyl-glyoxaline-2-mercaptan,** $C_3(CH_2NH_2)H_2N_2(SH)$, m.p. 188°, from diamino-acetone chloride and potassium thiocyanate. On treating with dilute nitric acid it yields 4- (or 5-) **Hydroxy-methyl-glyoxaline,** $C_3(CH_2OH)H_3N_2$, m.p. 94° (C. 1911, II. 30).

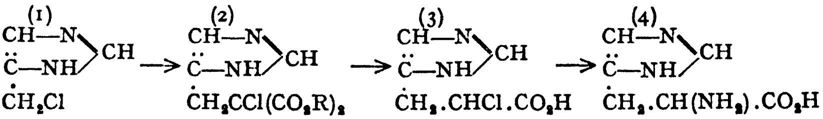
4,5-**Glyoxalinedicarboxylic - acid,** $C_3H_2(COOH)_2N_2$, from dioxy-tartaric acid, NH_3, and formaldehyde (A. Ch. ph. [6], **24,** 525), and by oxidation of benzo-glyoxaline (A. **273,** 339) separates on heating into CO_2 and glyoxaline.



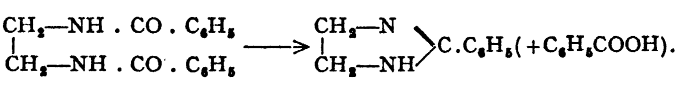
$CH\langle{}^{NH-\overset{*}{C}.CH_2.CH(NH_2)CO_2H}_{N-\overset{..}{C}H}$

l-Histidine, *β-5-Iminazolyl-α-aminopropionic acid,* $CH\langle{}^{NH-\overset{*}{C}.CH_2.CH(NH_2)CO_2H}_{N-\overset{..}{C}H}$ (C. 1904, II. 1289), flaky crystals, m.p. 253° with dec., $[\alpha]^{D}_{20}-39{\cdot}74°$, was first found in 1896 by A. Kossel among the disintegration products of the protamine sturin (B. **29,** R. 360), and also occurs in the hydrolysis of many proteins. By the action of nitrous acid histidine passes into the corresponding hydroxy acid, $C_3H_3N_2.CH_2.CH(OH)CO_2H+H_2O$, m.p. 204° with dec., which can be broken up into **glyoxaline-5-acetic acid,** $C_3H_3N_2.CH_2CO_2H+H_2O$, m.p. 220° with dec. **Glyoxaline-5-carboxylic acid,** $C_3H_3N_2CO_2H$, m.p. 286° with dec.; and finally glyoxaline itself (C. 1907, II. 1084). On the other hand, it can be reduced by means of HI and phosphorus to **glyoxaline-5-propionic acid,** $C_3H_3N_2.CH_2.CH_2CO_2H$, m.p. 209°. The latter acid can also be built up synthetically by the condensation of **glyoxyl-propionic acid,** $CHO.CO.CH_2.CH_2.CO_2H$ (Vol. I.), with ammonia and formaldehyde by method 1 (C. 1905, II. 830). Its azide can be converted by the method of Curtius into the 5-**aminoethylglyoxaline,** $C_3H_3N_2.CH_2CH_2NH_2$, the picrate of which melts at 234° with dec. (B. **40,** 3691). It can also be obtained from histidine by heating alone, or better with concentrated HCl to 270° (C. 1911, I. 1366), or by bacterial disintegration (C. 1910, II. 35). For other sources, see C. 1911, I. 493; and 1911, II. 30.

Synthesis of histidine (C. 1911, II. 760). 4- (5-) Chloromethylglyoxaline (1) from 4- (5-) hydroxymethyl-glyoxaline and PCl_5, yields with sodium-chloro-malonic ester 4- (5-) glyoxaline-chloro-malonic ester (2), which on saponification gives 4- (5-) glyoxaline-chloro-propionic acid (3). This is converted by NH_3 to $[d+l]$-histidine (4), which can be split up into the active components by means of tartaric acid:

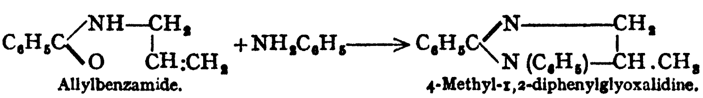


Hydroglyoxalines.—The glyoxalines cannot be reduced to hydroderivatives. *Dihydroglyoxalines,* or *glyoxalidines,* result (1) from the acidyl-compounds of ethylenediamine:



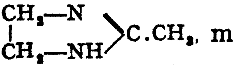
$$\begin{matrix}CH_2-NH.CO.C_6H_5\\ |\\ CH_2-NH.CO.C_6H_5\end{matrix}\longrightarrow\begin{matrix}CH_2-N\\ |\\ CH_2-NH\end{matrix}\rangle C.C_6H_5(+C_6H_5COOH).$$

(2) They are very probably the compounds formed from allylacetamide and allylbenzamide by means of the hydrochlorides of aromatic bases (B. **28,** 1665):



$$C_6H_5C\langle{}^{NH-CH_2}_{O\quad CH:CH_2}+NH_2C_6H_5\longrightarrow C_6H_5C\langle{}^{N-\!\!-\!\!-CH_2}_{N(C_6H_5)-CH.CH_3}$$

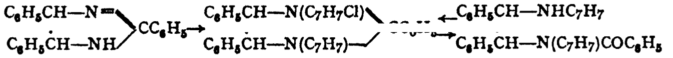
Allylbenzamide. 4-Methyl-1,2-diphenylglyoxalidine.



2-Methylglyoxalidine, *Lysidine,* $C_4H_8N_2=\begin{matrix}CH_2-N\\ |\\ CH_2-NH\end{matrix}\rangle C.CH_3$, melting at 105° and boiling at 195°–198°, is formed on heating ethylenediamine hydrochloride with sodium acetate. It forms a *very easily* *soluble uric acid salt*, and therefore has been recommended as a relief from gout (B. **27,** 2952). The homologous glyoxalidines—*e.g.*, **2-ethyl-, 2-propylglyoxalidine,** etc. (B. **28,** 1173, 1176)—behave similarly. Benzoyl chloride and alkali break down methylglyoxalidine into acetdibenzoylethylenediamine (B. **28,** 3068).

2-Phenylglyoxalidine, *Ethylenebenzamidine*, $C_3H_5(C_6H_5)N_2$, melting at 101°, is also obtained from ethylenediamine and thiobenzamide (B. **25,** 2135).

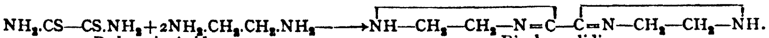
2,4,5-**Triphenyl-dihydro-glyoxaline, Amarine,** $C_{21}H_{18}N_2$, m.p. 133° (anhydrous), is formed by the transposition of hydrobenzamide. With halogen alkyls it forms dialkyl amaronium chlorides which are split up by alkalies into diphenylethylenediamine derivatives, from the hydrochlorides of which the amaronium bases are regenerated:



$$\begin{matrix}C_6H_5CH—N{=}\\C_6H_5CH—NH\end{matrix}\!\!>\!CC_6H_5 \rightarrow \begin{matrix}C_6H_5CH—N(C_7H_7Cl)\\C_6H_5CH—N(C_7H_7)\end{matrix} \begin{matrix}\leftarrow C_6H_5CH—NHC_7H_7\\ \rightarrow C_6H_5CH—N(C_7H_7)COC_6H_5\end{matrix}$$

The action of benzoyl chloride upon amarine is similar. On heating amarine with Na ethylate to 150° to 160°, or amarine hydrochloride to 340°, an isomeric *iso*-**amarine** is produced, m.p. 198°, also obtained synthetically from racemic dibenzoyldiphenylethylenediamine. Its relation to amarine is that of racemic acid to meso-tartaric acid. It has been split up into optically active components (C. 1900, I. 201, 1224). On oxidation amarine produces *lophine*. An analogous composition is shown by furfurin or trifuryl dihydro-glyoxaline.

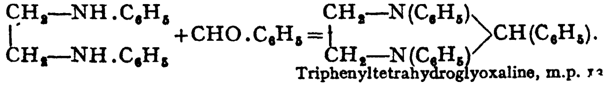
Bisglyoxalidine, $(C_3H_5N_2)_2$, melting at 290°–300°, is a condensation product of rubeanic acid and ethylenediamine (B. **24,** 1846):



$$NH_2.CS—CS.NH_2 + 2NH_2.CH_2.CH_2.NH_2 \longrightarrow NH—CH_2—CH_2—N{=}C—C{=}N—CH_2—CH_2—NH.$$

Rubeanic Acid. Bisglyoxalidin.

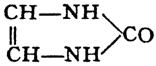
Tetrahydroglyoxalines have been obtained from ethylene aniline and aldehydes (B. **20,** 732):

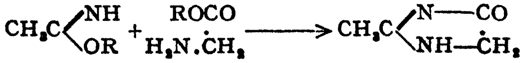


$$\begin{matrix}CH_2—NH.C_6H_5\\ |\\ CH_2—NH.C_6H_5\end{matrix} + CHO.C_6H_5 = \begin{matrix}CH_2—N(C_6H_5)\\ |\\ CH_2—N(C_6H_5)\end{matrix}\!\!>\!CH(C_6H_5).$$

Triphenyltetrahydroglyoxaline, m.p. 137°

We must include with the *keto-*, *thio-*, and *imino*-substitution products of hydroglyoxalines a series of cyclic urea-, thiourea-, and guanidine-derivatives, which for the most part have been already described with the fatty compounds.

1. *Ketoglyoxalidines, iminazolones*, or *ureïns*, result from the inner condensation of *a*-ureïdo-keto-compounds. **Iminazolone,**  $\begin{matrix}CH—NH\\ \|\\ CH—NH\end{matrix}\!\!>\!CO$, melting at 105°, is obtained from acetalyl urea (p. 103). Different ureïns have been obtained from benzoin and benzil by means of various ureas (compare B. **25,** 2357; **27,** 1083, 1144, 2203; Gaz. chim. Ital. **19,** 573; A. **368,** 156). 4,5-**Diphenyl-2-iminazolone,** m.p. 324° (see A. **330,** 249). 4-**Iminazolones,** like **2-methyl-4-iminazolone,** m.p. 141°, are formed by the condensation of imido-ethers with *a*-amino-aliphatic esters (J. pr. Ch. [2], **76,** 93; **82,** 50):



$$CH_3C\!<\!\begin{matrix}NH\\OR\end{matrix} + \begin{matrix}ROCO\\H_2N.CH_2\end{matrix} \longrightarrow CH_3C\!<\!\begin{matrix}N——CO\\NH—CH_2\end{matrix}$$

Glyoxaline Red, from acetylenedicarboxylic ester with 2 mol. benzamidine (see C. 1900, II. 92).

2. *Keto-* and *Thiotetrahydroglyoxalines* are the cyclic alkylene ureas and thioureas—*e.g.*, *ethylene urea* and *-thiourea* (I. 441, 452).

3. *Diketo-* and *iminoketotetrahydroglyoxalines* are found in the hydantoïns and *glycocyanidins*—*e.g.*, *hydantoïn*, *creatinine*, etc. (Vol. I.). To these also belongs the so-called **vinylidene oxanilides**, $\begin{matrix}CO—N(C_6H_5)\\ \dot{C}O—N(C_6H_5)\end{matrix}\rangle C{:}CH_2$, m.p. 209° (B. **33**, 613).

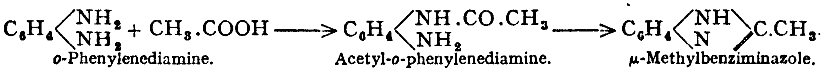
4. *Triketo-* and *iminodiketotetrahydroglyoxalines*: *oxalyl urea* or *parabanic acid* (I. 575) and *oxalyl guanidine* (B. **26**, 2552).

6. BENZOGLYOXALINES OR BENZIMINAZOLES.

The benziminazoles, sometimes called cyclic amidines, anhydro-bases, and aldehydins, contain the glyoxaline or iminazole ring in union with a benzene ring: $\begin{matrix}CH=CH—C—N\\ | \qquad\quad \| \\ CH=CH—C—NH\end{matrix}\rangle CH$. Their intimate connection with glyoxaline becomes very evident from the fact that benziminazole becomes glyoxaline dicarboxylic acid when it is oxidized (p. 103).

Formation of the Benziminazoles:

(1) By the condensation of *o*-phenylenediamines with carboxylic acids, or their anhydrides or chlorides. A loss of water occurs (Ladenburg, B. **8**, 677; **11**, 826). Acyl compounds are produced as intermediate products:

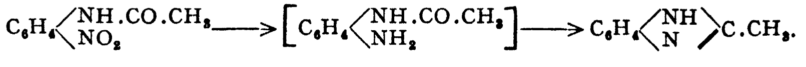


$$C_6H_4\langle\begin{matrix}NH_2\\NH_2\end{matrix} + CH_3.COOH \longrightarrow C_6H_4\langle\begin{matrix}NH.CO.CH_3\\NH_2\end{matrix} \longrightarrow C_6H_4\langle\begin{matrix}NH\\N\end{matrix}\rangle C.CH_3.$$

o-Phenylenediamine. Acetyl-*o*-phenylenediamine. *μ*-Methylbenziminazole.

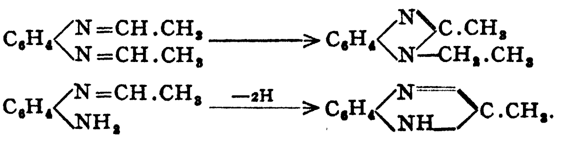
The diacidyl-*o*-phenylenediamines also yield benziminazoles (B. **23**, 1876; **25**, 1992). The anhydrides of dibasic acids react like those of the monobasic—*e.g.*, succinic anhydride and *o*-phenylenediamine form benziminazole-*μ*-propionic acid (B. **27**, 2773). The *o*-naphthylene-diamines behave like the *o*-phenylenediamines.

(2) Benziminazoles are also produced by the reduction of acylated *o*-nitranilines, when acylated *o*-phenylenediamines are also formed as intermediate products (Hobrecker, B. **5**, 920):



$$C_6H_4\langle\begin{matrix}NH.CO.CH_3\\NO_2\end{matrix} \longrightarrow \left[C_6H_4\langle\begin{matrix}NH.CO.CH_3\\NH_2\end{matrix}\right] \longrightarrow C_6H_4\langle\begin{matrix}NH\\N\end{matrix}\rangle C.CH_3.$$

(3) N-alkylic benziminazoles result when *aldehydes* act upon *o*-diamines (*aldehydins* of Ladenburg; B. **11**, 590). The dialkylidene-*o*-diamine, which probably first appears, rearranges itself at once into the *N*-alkyliminazole (B. **20**, 1585). The non-alkylated iminazole is produced as a by-product from the monoalkylidene body:



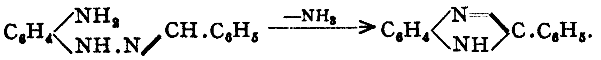
$$C_6H_4\langle\begin{matrix}N=CH.CH_3\\N=CH.CH_3\end{matrix} \longrightarrow C_6H_4\langle\begin{matrix}N\\N—CH_2.CH_3\end{matrix}\rangle C.CH_3$$

$$C_6H_4\langle\begin{matrix}N=CH.CH_3\\NH_2\end{matrix} \xrightarrow{-2H} C_6H_4\langle\begin{matrix}N=\!=\\NH—\end{matrix}\rangle C.CH_3.$$

Mono-alkylic *o*-diamines yield benziminazoles (B. **25**, 2826).

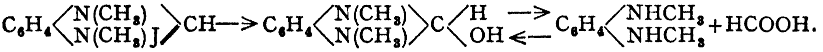
On the action of formaldehyde upon *o*-phenylene-diamine, see B. **32**, 245.

(4) μ-Phenylbenziminazole is formed from benzylidene *o*-amino-phenylhydrazine on heating with dilute mineral acids (B. **40**, 909):



$$C_6H_4\left\langle\begin{matrix}NH_2\\NH.N\end{matrix}\right. \!\!\diagup CH.C_6H_5 \xrightarrow{-NH_3} C_6H_4\left\langle\begin{matrix}N=\\NH\end{matrix}\right\rangle C.C_6H_5.$$

Properties.—The benziminazoles behave very much like the glyoxalines; however, the basic properties are slightly less than the salt-forming power of the imido-group. Most of the benziminazoles are soluble in aqueous alkalies. Alkyl residues are easily introduced into the imino group; acid residues, with more difficulty. The *N*-alkylated iminazoles add alkyl iodide. The iodo-alkylates are transformed into *N*-dialkyl-benziminazolinols by alkalies, with atomic migration. These are split up by boiling with NaHO into *o*-phenylene dialkylamines and formic acid, and can be synthesized from these components by heating:



$$C_6H_4\left\langle\begin{matrix}N(CH_3)\\N(CH_3)J\end{matrix}\right\rangle CH \longrightarrow C_6H_4\left\langle\begin{matrix}N(CH_3)\\N(CH_3)\end{matrix}\right\rangle C\left\langle\begin{matrix}H\\OH\end{matrix}\right. \overset{\longrightarrow}{\longleftarrow} C_6H_4\left\langle\begin{matrix}NHCH_3\\NHCH_3\end{matrix}\right. + HCOOH.$$

This fission is facilitated by nitro-groups in the benzene or glyoxaline nucleus, but hindered by alkyl substituents (J. pr. Ch. [2], **73**, 419). Benzoyl chloride and sodium hydroxide decompose even at 0°, just as in the case of the glyoxalines, the iminazole ring with the production of dibenzoylated *o*-diamines. They are very stable toward reducing and oxidizing agents. Certain derivatives of benziminazole can dye cotton without the help of mordants (B. **26**, 2760). In this respect they resemble the benzoxazoles and benzothiazoles.

The number of known benziminazoles is very great (see Kühling, Stickstoffhaltige Ortho-condensationsproducte, pp. 177-210).

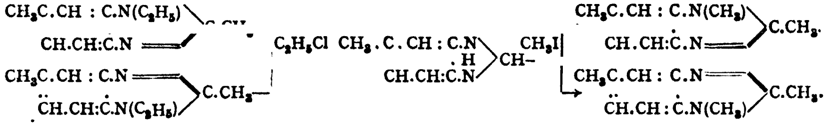
Benziminazole, *o-Phenyleneformamidine*, $C_6H_4\left\langle\begin{matrix}N-\\NH\end{matrix}\right\rangle CH$, melting at 167°, is obtained from formic acid and *o*-phenylenediamine, as well as by the action of chloroform and potash upon *o*-phenylenediamine (B. **28**, R. 392). Potassium permanganate oxidizes it in part to glyoxalinedicarboxylic acid. **μ-Methyl-benzimidazole,** *o-phenylene acetamidine*, $C_6H_4\left\langle\begin{matrix}N=\\NH\end{matrix}\right\rangle C.CH_3$, melts at 176°.

μ-Phenyl-benziminazole, *phenylenebenzamidine*, $C_6H_4\left\langle\begin{matrix}N=\\NH\end{matrix}\right\rangle C.C_6H_5$, melting at 291°, also results from the rearrangement of *o*-aminobenzophenoneoxime (B. **24**, 2386; **29**, R. 358).

μ-(*o*-Amino-phenyl)-benziminazole, $C_6H_4:CN_2H.C_6H_4NH_2$, m.p. 211°, gives with formic acid a bis-anhydro compound: **methenylaminophenyl benziminazole,** $\begin{matrix}N\!=\!\!=\!\!=C\ C_6H_4.N\\ \vdots \qquad\qquad \vdots\\ C_6H_4.N\!-\!\!-\!\!-\!\!-CH\end{matrix}$, m.p. 227°; nitrous acid produces the corresponding azimide, m.p. 208° (B. **32**, 1456). On μ- (*o*-, *m*-, and ***p*-amino-phenyl) benziminazole** and its transformations, see B. **34**, 2953.

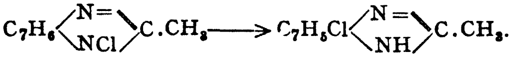
μ-Methyltoliminazole, o-*Toluylene Acetamidine*, $CH_3.C_6H_3.\langle{}^{N=}_{NH}\rangle C.CH_3$, melting at 199°, and obtained from 3:4-toluylenediamine with glacial acetic acid or acetaldehyde.

The two nitro-ethyltoluidines, $CH_3[1]C_6H_3[3]NO_2[4]NHC_2H_5$ and $CH_3[1]C_6H_3[4]NO_2[3]NHC_2H_5$, yield by method (2) two isomeric *N*-**ethyl-μ-methyltoliminazoles,** m.p. 87° and 93° respectively, which, on heating their hydrochlorides, split off ethyl-chloride and pass into the same μ-methyltoliminazole. With methyl iodide we obtain from μ-methyltoliminazole two isomeric *N*,**μ-dimethyltoliminazoles,** m.p. 132° and 142°, which are also obtained from the two *N*-methyl-*o*-toluylenediamines with glacial acetic acid, and on further action by methyl iodide pass into the same iodo-methylate, m.p. 221° (J. pr. Ch. [2], **73,** 424). The following scheme illustrates this:



Like the 4- (or 5-) alkylglyoxalines, the μ-methyltoliminazole belongs, therefore, to the virtually tautomeric compounds (compare B. **34,** 4202).

Silver nitrate precipitates the *silver salt*, $C_7H_6(C_2H_3N_2Ag)$. Chloride of lime replaces the imine hydrogen by chlorine, which readily exchanges its place with a benzene hydrogen atom:



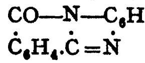
$$C_7H_6\langle{}^{N=}_{NCl}\rangle C.CH_3 \longrightarrow C_7H_5Cl\langle{}^{N=}_{NH}\rangle C.CH_3.$$

This chlorination may be continued until all of the hydrogen atoms of the benzene nucleus have been replaced by chlorine and there is finally obtained *N*-Chloro-*Bz*-trichloro-μ-methyl toliminazole.

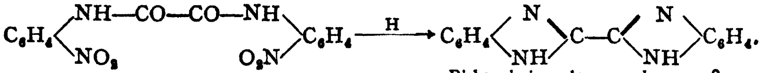
N-*Acetyl-μ-methyltoliminazole*, $C_7H_6(C_2H_3N_2.COCH_3)$, is formed when acetyl chloride acts upon the silver salt. The N-*benzoyl derivative*, melting at 92°, is formed from the base and benzoyl chloride, while benzoyl chloride and sodium hydroxide produce dibenzoyltoluylenediamine. μ-Methyltoliminazole condenses with benzaldehyde to *cinnamyl toliminazole*, $C_7H_6\langle{}^{N}_{NH}\rangle C.CH:CH.C_6H_5$, and with phthalic anhydride to a *phthalone* (compare quinophthalone), which is oxidized by potassium permanganate to *toliminazole-μ-carboxylic acid*, $C_8H_7N_2.COOH$.

1,2-**Naphthiminazole,** $C_{10}H_6(N_2H)CH$, m.p. 174°, gives on oxidation with chromic acid **Benziminazole-o-dicarboxylic acid,** $(COOH)_2C_6H_2(N_2H)CH$, m.p. 251° (B. **32,** 1312). *N*-**Methyl-**9,10-**phenanthriminazole,** *Epiosin*, $(C_6H_4)_2C_2(N_2.CH_3)CH$, m.p. 195°, is formed from 9,10-aminophenanthrol by heating with alcoholic methylamine solution. It acts physiologically like morphine (C. 1902, I. 1302). On polymeric benziminazoles, see B. **25,** 2712.

Benzylene-benziminazole, $\begin{matrix} CH_2—N—C_6H_4 \\ \dot{C_6H_4}.\dot{C}=\dot{N} \end{matrix}$, m.p. 210°, results from the condensation of *o*-phthal-aldehyde with *o*-phenylenediamine.

Gentle oxidation with $KMnO_4$ converts it into **o-Benzoylene-benziminazole,**  $\begin{matrix}CO-N-C_6H_4\\ \dot{C}_6H_4.\dot{C}=\dot{N}\end{matrix}$, yellow needles, m.p. 213°, the lactam of μ-phenyl iminazole-*o*-carboxylic acid, m.p. 266°, also obtained by the condensation of *o*-phenylenediamine with phthalic anhydride or *o*-phthalaldehydic acid, as well as by reduction of *o*-nitro-phthalanil (B. **42,** 4287).

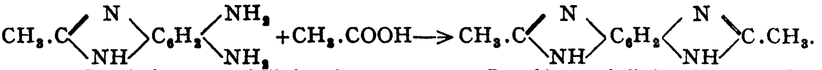
Bisbenziminazoles are made by reducing the *o*-nitro-oxanilides (A. **209,** 257):



$$C_6H_4\left<\begin{matrix}NH-CO-CO-NH\\ NO_2 \qquad\qquad\qquad O_2N\end{matrix}\right>C_6H_4 \xrightarrow{H} C_6H_4\left<\begin{matrix}N\\ NH\end{matrix}\right>C-C\left<\begin{matrix}N\\ NH\end{matrix}\right>C_6H_4.$$

Bisbenziminazole, m.p. above 300°.

Benzobisiminazoles are formed from the *o*-diaminobenziminazoles and carboxylic acids (B. **22,** 1652):

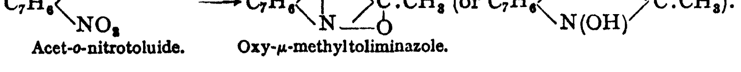


$$CH_3.C\left<\begin{matrix}N\\ NH\end{matrix}\right>C_6H_2\left<\begin{matrix}NH_2\\ NH_2\end{matrix}\right. + CH_3.COOH \longrightarrow CH_3.C\left<\begin{matrix}N\\ NH\end{matrix}\right>C_6H_2\left<\begin{matrix}N\\ NH\end{matrix}\right>C.CH_3.$$

o-Diaminobenzo-μ-methyliminazole. Benzobis-μ-methyliminazole, m.p. 145°.

Benziminazole hydrides, benziminazolines, are not known with certainty. The primary products resulting from the interaction of monoalkylic *o*-diamines and aldehydes are considered as such. They give up hydrogen and readily change to benziminazoles (B. **25,** 2827). The condensation products of acetoacetic ester with *o*-tolylenediamine (B. **25,** 606) behave similarly. Methylene iodide and dibenzenesulphonyl-*o*-phenylene-diamine yield **dibenzenesulphonylmethylene-o-phenylene-diamine,** $C_6H_4<\begin{matrix}N(SO_2C_6H_5)\\ N(SO_2C_6H_5)\end{matrix}>CH_2$, melting at 148°. It can be considered as a derivative of the simplest benziminazoline. In an attempt to split off the bezenesulphonic groups with hydrochloric acid it was resinified (B. **28,** R. 756).

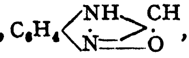
These substances can be considered as derivatives of hydrobenziminazoles, which result in the moderated reduction of acidylated *o*-nitranilines with ammonium sulphide (B. **22,** 1396):



$$C_7H_6\left<\begin{matrix}NH.COCH_3\\ NO_2\end{matrix}\right. \xrightarrow{H} C_7H_6\left<\begin{matrix}NH\\ N-O\end{matrix}\right>C.CH_3 \text{ (or } C_7H_6\left<\begin{matrix}N=\\ N(OH)\end{matrix}\right>C.CH_3\text{)}.$$

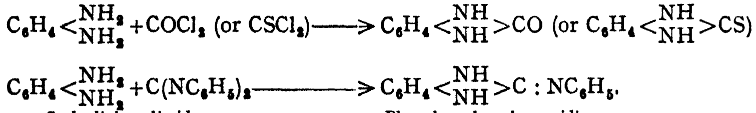
Acet-*o*-nitrotoluide. Oxy-μ-methyltoliminazole.

These are relatively stable bodies, which yield benziminazoles when they are distilled with zinc dust.

Oxibenziminazole,  $C_6H_4\left<\begin{matrix}NH\\ N\end{matrix}\right>\begin{matrix}CH\\ O\end{matrix}$, m.p. 210°, from *o*-nitroformanilide with Am_2S, easily transposes into the isomeric *o*-phenylene urea under the influence of various reagents. **μ-Methyl-oxibenziminazole,** m.p. 251°.

Benziminazolinols are formed from the alkyl halides of the *N*-alkyl benziminazoles with aqueous alkalies, and synthetically from *o*-phenylene dialkylamines with carboxylic acids (see p. 109). Their reversion to these components was discussed above. With HI they regenerate the iodo-alkylates of the *N*-alkyl benziminazoles, and by oxidation they easily pass into the stable *o*-phenylene ureas (see below). ***N*-Dimethyl-benziminazolinol,** $C_6H_4(NCH_3)_2CH(OH)$, m.p. 74°, is broken up by boiling with NaOH into formic acid and *o*-phenylenedimethylamine; the latter with acetic anhydride gives ***μ,N*-Trimethyl-benziminazolinol,** $C_6H_4(NCH_3)_2C(OH)CH_3$, m.p. 164°. ***m*-Nitro-*N*-dimethyl-benziminazolinol,** m.p. 128°, from the iodomethylate with soda or ammonia, is split up by mere treatment with cold NaOH. A compound not easily split up is ***N*-Phenyl-*N*-methyl-benziminazolinol,** m.p. 168°. *Bz*-1,3-**dimethyl-benzo-*N*-dimethyl-iminazolinol,** $(CH_3)_2C_6H_2(NCH_3)_2$-CH(OH), m.p. 135°, is only broken up by heating with alc. NaOH under pressure (B. **34,** 936, 4202; **36,** 3967; J. pr. Ch. [2], **73,** 419).

The cyclic phenylene ureas, -thioureas, and -guanidines are *keto-, thio-,* and *imidobenziminazolines,* which result from *o*-diamines with $COCl_2$ and $CSCl_2$ or CS_2, with urea and thiourea or ammonium sulphocyanide, with phenyl mustard oil and carbodi-imide:

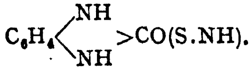


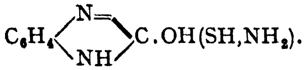
$$C_6H_4<^{NH_2}_{NH_2}+COCl_2\ (\text{or } CSCl_2) \longrightarrow C_6H_4<^{NH}_{NH}>CO\ (\text{or } C_6H_4<^{NH}_{NH}>CS)$$

$$C_6H_4<^{NH_2}_{NH_2}+C(NC_6H_5)_2 \longrightarrow C_6H_4<^{NH}_{NH}>C:NC_6H_5.$$

Carbodiphenylimide. Phenylenephenyl guanidine.

In many respects these bodies behave like oxy-, sulpho-, hydro-, and amino-derivatives of benziminazoles, and permit a choice from the two formulas:

I. 

II. 

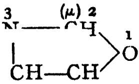
o-Phenyleneurea, *Benziminazolone,* $C_6H_4(N_2H_2CO)$, melting at 308°, is also obtained from *o*-aminophenylurethane (B. **12,** 1296; **23,** 1047). **o-Toluyleneurea,** $C_7H_6(N_2H_2)CO$, melting at 290°, also results in the saponification of *μ-ethoxytoliminazole,* $C_7H_6(N_2H)$: $C(OC_2H_5)$, melting at 163°. The latter is the reaction product of imidocarbonic ester and *o*-toluylenediamine.

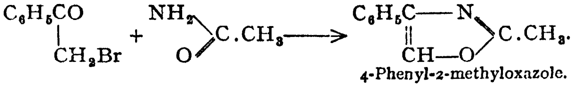
o-Phenylene-thio-urea, *Thiobenziminazoline,* $C_6H_4(N_2H_2)CS$, melting at 298° with decomposition, is obtained from phenylenediamine sulphocyanide (A. **221,** 9; **228,** 244).

o-Phenylene-phenylguanidine, *μ-Anilinobenziminazoline,* C_6H_4-$(CN_3H_2C_6H_5)$, melting at 188°, is obtained from carbodiphenylimide and *o*-phenylenediamine.

The *oxazoles* and *thiazoles* correspond to the *iminazoles.* The latter were regarded as cyclic amidines, and the former may be looked upon as cyclic imido-ethers and alkylene thioamides. As a rule, these bodies are as little changed by reduction to hydride bases as the glyoxalines or iminazoles; they remain unaltered or are decomposed (compare B. **29,** 2381).

7. OXAZOLES OR FURO-[b]-MONAZOLES.

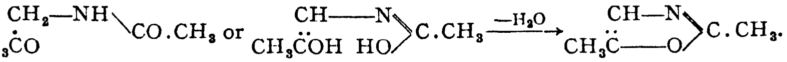
The *oxazoles* or *furo*-[b]-*monazoles*,  are isomeric with the isoxazoles (furo-[*a*]-monazoles, p. 98). Oxazoles are produced (1) by the condensation of α-haloid ketones with acid-amides (B. **20,** 2576; **21,** 2195):



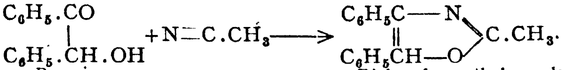
4-Phenyl-2-methyloxazole.

It may be assumed that here the ketone and amide react in the hydroxyl form.

(2) From acylated α-amino-ketones by the action of PCl_5 or conc. H_2SO_4 (B. **43,** 1283; C. 1910, I. 658; see furans):

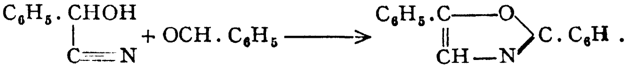


(3) When concentrated sulphuric acid acts upon benzoin and acid nitriles (B. **26,** R. 496):



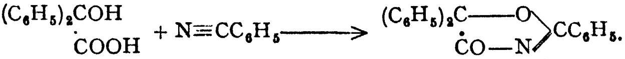
Benzoin. 4,5-Diphenyl-2-methyloxazole.

(4) When hydrochloric acid gas acts upon mandelo-nitrile (and homologues) and benzaldehydes (B. **29,** 2097):



2,5-diphenyloxazole.

Similarly, from benzilic acid and benzonitrile we obtain with conc. sulphuric acid **triphenyl oxazolone:**



Triphenyl-oxazolone.

The oxazoles are feeble bases. They break down into acids and amines on evaporation with hydrochloric acid. Oxidants and reducing agents frequently rupture the oxazole ring with great ease. The parent substance of the group is not known.

4-Phenyloxazole, $C_3H_2(C_6H_5)NO$, melting at 46° and boiling at 222°, is made from formamide and bromacetophenone. **4-Phenyl-** and **4,5-Diphenyl-2-methyloxazole,** melting at 45° and boiling at 242°, and melting at 44° and boiling at 192°–195° (15 mm.) (see above). **5-Methyl-2-phenyloxazole,** from benzamide and chloracetone, is converted by alcoholic ammonia into *phenylmethylglyoxaline.*

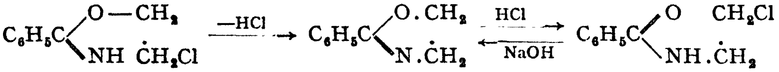
2,5-Dimethyloxazole, b.p. 108°, from acetamide and chloracetone, or from acetamino-acetone and PCl_5, gives on reduction **2,5-dimethyl-**

oxazolidine, b.p. 159°, and on oxidation 2-**methyloxazole-5-carboxylic acid,** m.p. 288° (B. **30,** 2254). 5-**Methyl-2-phenyloxazole,** b.p. 255°, and 5-**phenyl-2-methyloxazole,** m.p. 59°, b.p. 255°, from benzoyl aminoacetone and acetaminoacetophenone respectively.

2,5-**Diphenyloxazole,** melting at 74° and boiling above 360°, is formed from benzamide and phenylbromacetaldehyde by method 1, and, together with benzalmandelic amide, from the nitrile of mandelic acid and benzaldehyde by method 3 (B. **29,** 205). Chromic acid oxidizes it to *phenylglyoxylbenzamide,* $C_6H_5CO.CO.NH.CO.C_6H_5$, while sodium and alcohol reduce it to the amine, $C_6H_5CH_2.NH.CH_2.CH(OH)C_6H_5$. Nitric acid apparently produces a nitrodiphenyloxazole. It is converted into diphenyliminazole when heated with ammonia.

Triphenyloxazole, *Benzilam,* $(C_6H_5)_3C_3NO$, m.p. 115°, is formed from benziles with concentrated ammonia (B. **35,** 4137).

Dihydro-oxazoles, oxazolines result from the condensation of *β*-halogen alkylamides of carboxylic acids by means of alkalies (B. **22,** 2220). Benzimido-chlorethyl-ether passes into the chlorohydrate of phenyl oxazoline even on gentle heating, and the latter, at 100°, transposes further into chlorethyl benzamide (B. **35,** 164):



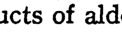
$$C_6H_5C\begin{smallmatrix}O-CH_2\\NH\ \ CH_2Cl\end{smallmatrix} \xrightarrow{-HCl} C_6H_5C\begin{smallmatrix}O.CH_2\\N.CH_2\end{smallmatrix} \underset{NaOH}{\overset{HCl}{\rightleftarrows}} C_6H_5C\begin{smallmatrix}O\ \ \ CH_2Cl\\NH.CH_2\end{smallmatrix}$$

2-**Phenyloxazoline,** boiling at 243°, is broken down, in the reduction with sodium and amyl alcohol, to hydroxyethylbenzylamine, $OHCH_2.CH_2.NHCH_2C_6H_5$ (B. **29,** 2382).

2-**Methyloxazoline** is an oil. Its *picrate* melts at 159° (B. **23,** 2502).

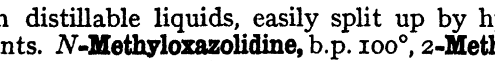
4-**Methyl-2-phenyloxazoline,** boiling at 244°, is obtained from *β*-brompropylbenzamide, also from allylbenzamide, $C_6H_5.CO.NH.CH_2.CH:CH_2$, with concentrated sulphuric acid (B. **26,** 2840) (compare glyoxalidines).

Keto-dihydro-oxazoles or *oxazolones* are represented by the lactone-like anhydrides of the *α*-benzoyl-amino-aliphatic acids—*e.g.,*



$$\begin{smallmatrix}O-CO\\N-CHCH_3\end{smallmatrix}.$$

Tetrahydro-oxazoles, *oxazolidines.* These are the condensation products of aldehydes with amino-alcohols (B. **34,** 3484):

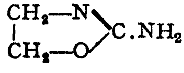


$$RCHO + \begin{smallmatrix}HO.CH_2\\R'NH.CH_2\end{smallmatrix} \longrightarrow RCH\begin{smallmatrix}O-CH_2\\NR'.CH_2\end{smallmatrix}$$

They form distillable liquids, easily split up by hydrolysis into their components. *N*-**Methyloxazolidine,** b.p. 100°, 2-**Methyloxazolidine,** b.p. 141°, 2,3-**Dimethyloxazolidine,** b.p. 109° (compare 2,5-Dimethyl-oxazolidine), 2-**Phenyloxazolidine,** b.p. 284°.

Amino-oxazolines or *iminotetrahydro-oxazoles* are the so-called allylene-*ψ*-ureas.

Ethylene-*ψ*-urea, 2-*amino-oxazoline,*

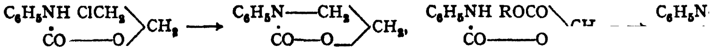


$$\begin{smallmatrix}CH_2-N\\CH_2-O\end{smallmatrix}C.NH_2$$

; its *picrate* melts at 158°.

Propylene-*ψ*-urea, 2-*amino*-5-*methyloxazoline;* its *picrate* melts at 186°. These compounds result from the action of potassium cyanate upon β-bromethyl- and -propylamine. **4,5-Diphenyl-2-aminoxazoline**, melting at 154°, is formed from diphenylhydroxyethylamine and potassium cyanate (B. **28**, 1899).

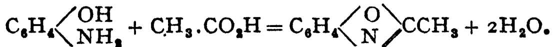
Derivatives of a keto-tetrahydro-oxazole are formed from carbamino β-halogenalkyl esters by rejection of HCl (C. 1911), and diketo-derivatives from the phenyl urethanes of the α-oxy-acid esters (C. 1898 II. 480; 1902, II. 342):



$$\genfrac{}{}{0pt}{}{C_6H_5NH\ ClCH_2}{\dot{C}O\text{——}O}>CH_2 \longrightarrow \genfrac{}{}{0pt}{}{C_6H_5N\text{——}CH_2}{\dot{C}O\text{—}O\text{—}}>CH_2,\quad \genfrac{}{}{0pt}{}{C_6H_5NH\ ROCO}{\dot{C}O\text{——}O}\diagdown CH \longrightarrow C_6H_5N$$

8. BENZOXAZOLES.

These, like the production of benziminazoles from *o*-phenylene diamines, result upon heating *o*-aminophenols with carboxylic acids:



$$C_6H_4<\genfrac{}{}{0pt}{}{OH}{NH_2} + CH_3.CO_2H = C_6H_4<\genfrac{}{}{0pt}{}{O}{N}>CCH_3 + 2H_2O.$$

o-Aminophenol. μ-Methylbenzoxazole.

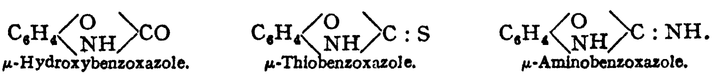
The benzoxazoles, also called alkenylaminophenols, are weak bases. They are resolved into their components on digesting them with acids. Some benzoxazole derivatives are substantive cotton dyes (B. **28**, 1127).

Benzoxazole, *Methenylaminophenol*, $C_6H_4<\genfrac{}{}{0pt}{}{O}{N}>CH$, melts at 31° and boils at 183°. It is volatile with water vapour, and is formed by heating *o*-amino-phenol with formic acid, or heating *o*-formylamino-phenol to 160°–170°. It is split up again to formylamino-phenol on merely boiling in water. It resembles the isomeric anthranil (B. **36**, 2054). Heated with CH_3I it forms an iodo-methylate, m.p. 183° with dec., which is decomposed by dilute HCl with formation of *N*-methyl-*o*-amidophenol.

μ-Methylbenzoxazole, *ethenylaminophenol*, boils at 201°. **μ-Phenylbenzoxazole**, melting at 103°, is also formed in the reduction of benzoyl-*o*-nitrophenol (B. **9**, 1526; **29**, R. 358; A. **210**, 384).

μ-Aminophenyltoluoxazole, $CH_3.C_6H_3<\genfrac{}{}{0pt}{}{N}{O}>C.C_6H_4NH_2$, melting at 188°, is produced in the reduction of *p*-nitrobenzoyl-*m*-nitro-*p*-cresol. By combination of its diazo-derivative with β-naphthol, etc., carmine-red, acid-stable substantive cotton dyes are produced.

Oxy- and *thio*-derivatives of the benzoxazoles are obtained from *o*-aminophenols with $COCl_2$ or $ClCO_2R$ and CS_2 or $CSCl_2$. *Amino*-derivatives result on heating thio- or oxy-compounds with amines. Here, as in the case of analogous benziminazole compounds, two formulas may be considered for these bodies:



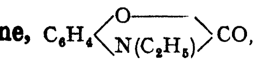
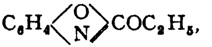
$$C_6H_4<\genfrac{}{}{0pt}{}{O}{N}>C(OH) \qquad C_6H_4<\genfrac{}{}{0pt}{}{O}{N}>C(SH) \qquad C_6H_4<\genfrac{}{}{0pt}{}{O}{N}>C(NH_2)$$

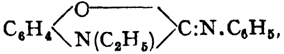
$$C_6H_4<\genfrac{}{}{0pt}{}{O}{NH}>CO \qquad C_6H_4<\genfrac{}{}{0pt}{}{O}{NH}>C:S \qquad C_6H_4<\genfrac{}{}{0pt}{}{O}{NH}>C:NH.$$

μ-Hydroxybenzoxazole. μ-Thiobenzoxazole. μ-Aminobenzoxazole.

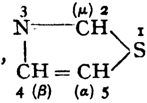
Isomeric alkyl compounds are derived from the two forms of μ-hydroxybenzoxazole, which may be distinguished as *lactim* and *lactam* *ethers* or O- and N-alkyl derivatives. The aminobenzoxazoles exhibit similar conditions.

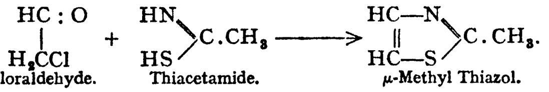
μ-Hydroxybenzoxazole, *Carbonylaminophenol,* $C_7H_5NO_2$, melting at 137°, is insoluble in alkalies. Ethyl iodide converts it into an *N*-ethyl derivative. **Benzoyl** derivative, m.p. 174° (C. 1898, I. 1277).

N-**Ethylbenzoxazolone,**  $C_6H_4<\begin{matrix}O\\N(C_2H_5)\end{matrix}>CO$, melts at 29°. **μ-Ethoxybenzoxazole,**  $C_6H_4<\begin{matrix}O\\N\end{matrix}>COC_2H_5$, is formed from iminocarbonic ester and *o*-aminophenol (B. **19,** 2655). A **dibromocarbonyl aminophenol,** m.p. 255°, is formed from salicylic acid amide with KOBr (C. 1900, I. 256). **μ-Thiobenzoxazole,** C_7H_5NSO, melting at 193°–196°, is soluble in alkalies and ammonia. It is obtained from aminophenol hydrochloride by the action of potassium xanthogenate; also from *o*-hydroxyazobenzene and CS_2.

μ-Anilinobenzoxazole, $C_7H_5N_2O(C_6H_5)$, melting at 137°, is produced simultaneously. The latter is also formed on heating thiobenzoxazole with aniline. **μ-Aminobenzoxazole,** $C_7H_5N_2O$, melting at 130°, is isomeric with *o*-phenylene urea (p. 112). It results on splitting off hydrogen sulphide from *o*-hydroxyphenylthiourea by means of mercuric oxide. **μ-Phenylimino-*N*-ethylbenzoxazolone,**  $C_6H_4<\begin{matrix}O\\N(C_2H_5)\end{matrix}>C:N.C_6H_5$, is formed from *N*-ethylbenzoxazolone and aniline (J. pr. Ch. [2], **42,** 450).

9. THIAZOLES OR THIO-[b]-MONAZOLES.

Just as the oxazoles are prepared from acid-amides, so the thiazoles or *thio*-[b]-*monazoles,*  are obtained from the thio-amides and *α*-haloid ketone derivatives:



Further, thiazole and its homologues result from the action of nitrous acid and alcohol upon μ-aminothiazoles, just as the benzene hydrocarbons are obtained from the anilines.

Behaviour.—Thiazole may be derived from pyridine, just as thiophen is derived from benzene—*i.e.*, by imagining a CH:CH-group replaced by sulphur. Accordingly, the thiazoles show a like agreement or similarity in their physical and in part in their chemical properties with the pyridines, just as the thiophens do with the benzenes.

The thiazoles are tertiary bases, forming addition-products with alkyl iodides. As a rule, they are stable toward oxidizing agents; chloric acid, however, destroys them.

Thiazole, C_3H_3NS, boiling at 117°, has an odour like that of pyridine. It results when N_2O_3 and alcohol act upon μ-aminothiazole. $C_3H_3NS.HCl.AuCl_3$ melts with decomposition at 248°–250°. C_3H_3NS.-

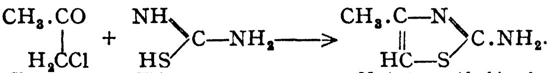
$HgCl_2$ melts at 202°–204°. 5-**Methylthiazole,** $C_3H_2(CH_3)NS$, boiling at 232°, is obtained from its amino-compound and by distilling methyl oxythiazole with zinc-dust (A. **250,** 279). The isomeric 2-**methyl thiazole,** boiling at 128°, with an odour like picoline, is prepared from monochloracetone and thiacetamide. 2,5-**Dimethylthiazole,** boiling at 143°, from chloracetone and thiacetamide, when reduced by sodium and alcohol is resolved into ethylpropylamine and hydrogen sulphide. It condenses, like the α-methylated pyridines, with formic aldehyde to an alkine, $C_3HNS(CH_3)(CH_2.CH_2OH)$ (B. **27,** 1009).

Trimethylthiazole, $C_3(CH_3)_3NS$, melts at 167°. 5-**Phenylthiazole** melts at 52° and boils at 273°. **Triphenylthiazole,** melting at 87°, is formed from thiobenzamide and bromdesoxybenzoin or desylbromide.

Halogeno-thiazoles are prepared by acting with concentrated haloid acids upon diazothiazoles:

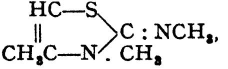
2-**Chlorothiazole** boils at 145° and 2-**bromothiazole** boils at 171°.

2-*Aminothiazoles* result from the action of α-haloid keto-compounds upon thioureas:

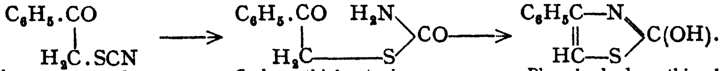

α-Chloracetone. Thiourea. 4-Methyl-2-amidothiazol.

Substances are formed from the symmetrical dialkylic thioureas which are derived from *iminothiazoline.* Consult A. **265,** 110, for isomeric monalkylaminothiazoles.

The aminothiazoles are similar to the anilines. They can be converted into diazo-compounds, and through these into haloid thiazoles, thiazoles, thiazole-azo-dyes, etc.

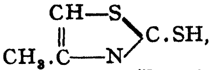
2-**Amino-thiazole,** $C_3H_2(NH_2)NS$, melting at 90°, may be prepared from dichlor-ether and thiourea. Its *nitrate* is converted by N_2O_3 into **diazothiazole hydrate,** $C_3H_2(.N:NOH)NS$, which yields yellow to brown-coloured azo-dyes with resorcinol, naphthol, etc. (A. **246,** 40). **Methyl-2-amino-thiazole,** $C_3H(CH_3)(NH_2)NS$, melting at 42° and boiling at 136° (30 to 40 mm.), is formed from chloracetone and thiourea or ammonium sulphocyanide (B. **20,** 3127). **Phenyl-2-aminothiazole,** $C_3H(C_6H_5)(NH_2)NS$, from ω-chloracetophenone, yields *phenyldiazothiazole hydrate* (A. **261,** 14). 3,4-**Dimethyl-2-methylimidothiazoline,**  melting at 96°, is obtained from chloracetone and symmetrical dimethylthiourea.

Hydroxythiazoles are obtained from α-sulphocyano-ketones by the action of alkali:


Sulphocyano-acetophenone. Carbamothiolacetophenone. 4-Phenyl-2-hydroxythiazol.

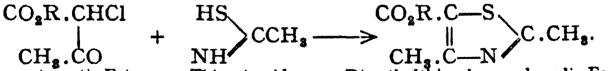
4-**Methyl-2-hydroxythiazole,** $C_3H(CH_3)(OH)NS$, melting at 160°, results from the exit of carbon dioxide from its carboxylic acid, and also when alkalies act upon sulphocyanacetone (A. **259,** 297; B. **25,** 3652). 5-**Phenyl-2-hydroxythiazole** melts at 204° (A. **249,** 16) (see above).

Mercaptothiazoles result upon heating α-chloroketones with ammonium dithiocarbaminate:

4-**Methyl**-2-**mercapto-thiazole,**  melts at 90°.

2-**Phenylmercapto-thiazole** melts at 168° (B. **26,** 604).

Thiazole Carboxylic Acids.—Their esters are produced in the condensation of chloracetoacetic ester, chloroxaloacetic ester, etc., with thioamides:



α-Chloracetoacetic Ester. Thiacetamide. Dimethylthiazole-5-carboxylic Ester.

Furthermore, the *amino-, oxy-,* and *mercapto-thiazole* carboxylic acids are formed by reactions similar to those employed for the amino-, oxy-, and mercapto-thiazols, if instead of the ketone derivatives the corresponding ketone carboxylic acids are introduced into the reactions.

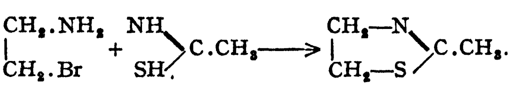
4-**Methylthiazole**-5-**carboxylic acid,** $C_3(CH_3)HNS(COOH)$, melts at 257°. Its ester is obtained from aminomethylthiazole carboxylic ester (see below) by converting it into chlorothiazolecarboxylic ester and then reducing the latter.

2-**Methyl**-4,5-**thiazoledicarboxylic acid,** $C_3(CH_3)(COOH)_2NS$, melts with decomposition at 169°. It is formed from chloroxaloacetic ester and thiacetamide. 2-**Methyl**-4-**thiazylacetic ester,** $C_3H(CH_3)(CH_2.CO_2R)NS$, boiling at 239°, is formed from γ-bromacetoacetic ester and thiacetamide.

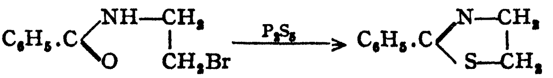
2-**Aminothiazole**-4-**carboxylic acid, sulphuvinic acid,** $C_3HSN(NH_2)$-$COOH(+2H_2O)$, decomposes at 245°, and is formed from dibromopyroracemic acid. Its *ester*, melting at 173°, is produced from monobromopyroracemic ester and thiourea (A. **261,** 25).

2-**Amino-methylthiazole**-4-**carboxylic ester,** melting at 175°, is obtained from α-chloracetoacetic ester and thiourea. Its *diazohydrate* melts at 100° with decomposition. 2-**Hydroxy**-4-**methylthiazolecarboxylic ester,** $C_3(OH)(CH_3)SN.COOC_2H_5$, melting at 128°, is formed from α-sulphocyanacetoacetic ester (A. **259,** 284, 298). 2-**Mercapto**-4-**methylthiazolecarboxylic ester,** $C_3(SH)(CH_3)SN.COOC_2H_5$, melting at 141°, is formed from α-chloracetoacetic ester and ammonium dithiocarbaminate (B. **26,** R. 604).

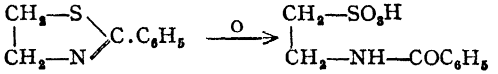
Dihydrothiazoles or *thiazolines* are synthesized from (1) alkylene haloids, or β-haloid alkylamines and thioamides (B. **24,** 783; **29,** 2610):



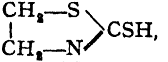
(2) By the action of P_2S_5 upon acidyl-β-bromalkylamides (B. **26,** 1328):

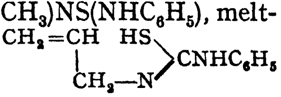


The thiazolines are much more readily decomposed than the thiazoles. 2-**Methylthiazoline,** boiling at 145°, on evaporation with hydrochloric acid, becomes β-amino-ethyl mercaptan. 2-**Phenylthiazoline,** boiling at 276°, is obtained from benzoyl-β-bromethylamide by the action of P_2S_5. It yields benzoyltaurine when it is oxidized:



$$\begin{array}{l}CH_2{-}S\\ |\\ CH_2{-}N\end{array}\!\!>C.C_6H_5 \xrightarrow{O} \begin{array}{l}CH_2{-}SO_3H\\ |\\ CH_2{-}NH{-}COC_6H_5\end{array}$$ (B. **23**, 158).

5-Methyl-2-tolylthiazoline, $C_3H_3(CH_3)(C_7H_7)NS$, boiling at 295°, is made from β-brompropyltolylamide and P_2S_5. **Thiazoline-2-mercaptan,**  $\begin{array}{l}CH_2{-}S\\ |\\ CH_2{-}N\end{array}\!\!>CSH$, melting at 107°, is prepared from bromethylamine and CS_2 (B. **22**, 1152), as well as by the action of carbon bisulphide upon vinylamine, $CH_2:CH.NH_2$ (B. **28**, 2932).

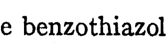
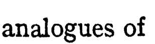
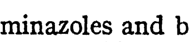
The alkylene derivatives of *pseudo*-thiourea, previously discussed, are *aminothiazolines*. They have mostly been obtained by rearrangement of allyl thioureas (*thiosinamines*, I. 409). **2-Anilino-5-methylthiazoline,** N-*Phenylpropylene-ψ-thiourea*, $C_3H_3(CH_3)NS(NHC_6H_5)$, melting at 117°, is made from allyl phenylthiourea,  $\begin{array}{l}CH_2{=}CH\quad HS\\ |\\ CH_2{-}N\end{array}\!\!>CNHC_6H_5$ (B. **22**, 2991).

2-Piperidyl-5-methylthiazoline, $C_3H_3(CH_3)NS(NC_5H_{10})$, boiling at 277°, is obtained from allylpiperidylthiourea (B. **24**, 265). **2-Methylamino-4,5-diphenylthiazoline,** $C_3H_2(C_6H_5)_2NS(NHCH_3)$, melting at 155°, is derived from diphenylhydroxyethylamine and methyl mustard oil (B. **28**, 1900).

The following are derivatives of tetrahydrothiazole:

2,4-Diketotetrahydrothiazole (I.), melting at 112°. It results on evaporating sulphocyanacetic acid or sulphocyanacetamide with acids (B. **26**, R. 324; I. 469).

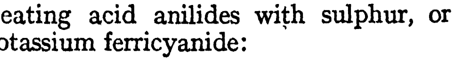
2-Thio-4-keto-thiazolidine, rhodaninic acid (II.), from chloracetic acid and ammonium sulphocyanate (C. 1903, I. 283; 1908, II. 1038), and **4-keto-2-imido-thiazolidine,** *pseudo*-thiohydantoïn (III.), m.p. 71°:

(I)  $\begin{array}{l}CH_2{-}S\\ \cdot\\ CO.NH\end{array}\!\!>CO.$ (II)  $\begin{array}{l}CH_2{-}S\\ \cdot\\ CO.NH\end{array}\!\!>CS.$ (III)  $\begin{array}{l}CH_2{-}S\\ \cdot\\ CO.NH\end{array}\!\!>C:NH.$

2-Imido-4-keto-thiazolidine acetic acid, m.p. 216° with decomposition, from chloro-succinic acid and thiourea (B. **27**, R. 742), gives the *diketo acid* m.p. 169° on hydrolysis.

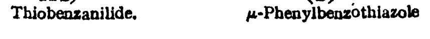
10. BENZOTHIAZOLES.

The benzothiazoles, the analogues of the benziminazoles and benzoxazoles (*anhydro-bases*) are prepared (1) from *o*-aminothiophenols (II. 209) and carboxylic acids (their chlorides or anhydrides) by the exit of water (A. W. Hofmann, B. **13**, 1224):



$$C_6H_4\!<\!\begin{array}{l}SH\\ NH_2\end{array} + COOHR \longrightarrow C_6H_4\!<\!\begin{array}{l}S\\ N\end{array}\!\!>C.R.$$

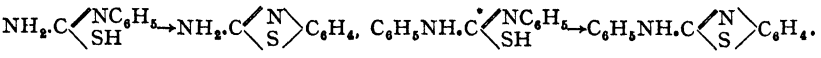
(2) Upon heating acid anilides with sulphur, or oxidizing thioanilides with potassium ferricyanide:



$$\underset{\text{Thiobenzanilide.}}{\begin{array}{l}C_6H_5{-}N\\ \quad HS\end{array}\!\!>C.C_6H_5} \xrightarrow{O} \underset{\mu\text{-Phenylbenzothiazole}}{C_6H_4\!<\!\begin{array}{l}N\\ S\end{array}\!\!>C.C_6H_5.}$$

Phenylbenzothiazole is also produced on heating benzylamine with sulphur. Hydrogen sulphide is evolved and thiobenzanilide is first formed, which then reacts in the sense above indicated (A. **259,** 300).

Similarly, the action of Br in chloroform solution upon arylthioureas produces cyclic phenylene-ψ-thioureas and μ-aminobenzothiazoles (B. **36,** 3121).

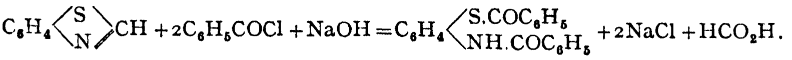


$$NH_2.C\left\langle\begin{matrix}NC_6H_5\\SH\end{matrix}\right. \rightarrow NH_2.C\left\langle\begin{matrix}N\\S\end{matrix}\right\rangle C_6H_4,\quad C_6H_5NH.C\left\langle\begin{matrix}NC_6H_5\\SH\end{matrix}\right. \rightarrow C_6H_5NH.C\left\langle\begin{matrix}N\\S\end{matrix}\right\rangle C_6H_4.$$

The benzothiazoles are feeble bases; their odour resembles that of quinoline. Fusion with caustic potash resolves them into aminothiophenols and carboxylic acids.

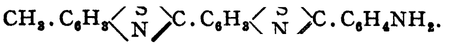
Different benzothiazole derivatives are important as *substantive cotton dyes.*

Benzothiazole, *methenylaminothiophenol,* $C_6H_4(NSCH)$, b.p. 234°, is formed (1) from *o*-aminothiophenol and formic acid; (2) from formanilide and sulphur; (3) from dimethylaniline on heating with sulphur (B. **31,** 3164); (4) from *o*-nitrophenylthioglycollic acid on heating with concentrated NaOH (M. **28,** 270). Benzoyl chloride and NaHO splits up benzo-thiazole (like benziminazole) into dibenzoyl-*o*-amino-phenol and formic acid (B. **38,** 3430):



$$C_6H_4\left\langle\begin{matrix}S\\N\end{matrix}\right\rangle CH + 2C_6H_5COCl + NaOH = C_6H_4\left\langle\begin{matrix}S.COC_6H_5\\NH.COC_6H_5\end{matrix}\right. + 2NaCl + HCO_2H.$$

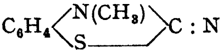
Benzisothiazole, $C_6H_4\left\langle\begin{matrix}CH\\|\\N\end{matrix}\right\rangle S$, boiling at 242°, is isomeric with benzothiazole. It is formed in the reduction of the *o*-nitrobenzyl ester of carbaminthiolic acid or of *o*-nitrobenzylmercaptan (II. 251) (B. **28,** 1028; **29,** 160). **μ-Methylbenzothiazole,** $C_6H_4(NSC_2H_3)$, boils at 238°. **μ-Phenylbenzothiazole** melts at 114°. **μ,*p*-Amino-phenyl-toluthiazole, Dehydrothiotoluidine,** $CH_3 . C_6H_3\left\langle\begin{matrix}N\\S\end{matrix}\right\rangle C.C_6H_4.NH_2$, melting at 191°, is produced when thiotoluidine is heated with sulphur. Its *trimethyl-ammonium chloride* derivative is the dye **Thioflavine.** Dehydrotoluidine, when further heated with thiotoluidine and sulphur, yields the base of the dye **Primuline:**



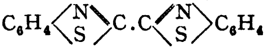
$$CH_3.C_6H_3\left\langle\begin{matrix}S\\N\end{matrix}\right\rangle C.C_6H_3\left\langle\begin{matrix}S\\N\end{matrix}\right\rangle C.C_6H_4NH_2.$$

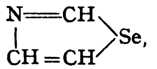
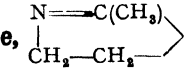
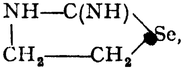
A series of benzothiazole derivatives has been obtained from "**chlor-phenyl-mustard oil,**" or **μ-chlorbenzothiazole,** $C_6H_4\left\langle\begin{matrix}S\\N\end{matrix}\right\rangle CCl$, melting at 24° and boiling at 248°. It results when PCl_5 acts upon phenyl-mustard oil. The reduction of chlorphenyl-mustard oil leads to benzothiazole; with alcohol we get μ-hydroxybenzothiazole; with sodium ethylate, μ-ethoxybenzothiazole; with sodium sulphydrate, sulphydro-, with ammonia, amino-, and with aniline, anilino-benzothiazole. **μ-Hydroxybenzothiazole,** $C_6H_4(NSCOH)$, melting at 136°, is formed from chlorocarbonic ester and aminothiophenol. **μ-Ethoxybenzothiazole,** $C_6H_4(NSCO_2H_5)$, melting at 25° and boiling above 360°, results upon oxidizing phenylthiourethane with potassium ferricyanide.

μ-Sulphydrobenzothiazole, $C_6H_4(NSC.SH)$, melting at 179°, is also obtained from aminothiophenol and CS_2; from azobenzene with CS_2; from phenyl-mustard oil and sulphur, etc. (B. **24,** 1403). **μ-Amino-benzothiazole,** $C_6H_4(NSC.NH_2)$, melts at 129° (B. **13,** 11). **μ-Anilino-benzothiazole,** $C_6H_4(NSC.NHC_6H_5)$, melting at 159°, is also formed from azobenzene and phenyl-mustard oil (B. **24,** 1410). Amino-benzo-thiazole with methyl iodide yields *N*-**methyl-imino-benzo-thiazoline,**

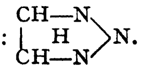

$C_6H_4\left\langle\begin{matrix}N(CH_3)\\S\end{matrix}\right\rangle C:NH$, m.p. 123° (B. **43,** 1519).

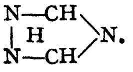
Benzo-thiazole-carboxylic acid, $C_6H_4(NSC)CO_2H$, melts at 108°, decomposing into CO_2 and benzo-thiazole. It is formed by the oxidation of thio-oxanilinic acid, $C_6H_5NH.CSCO_2H$, with potassium ferri-cyanide in alkaline solution (B. **37,** 3710).

Bis-benzothiazole,

$C_6H_4\left\langle\begin{matrix}N\\S\end{matrix}\right\rangle C.C\left\langle\begin{matrix}N\\S\end{matrix}\right\rangle C_6H_4$ (B. **29,** R. 87), is produced when sulphur is heated with acetanilide.

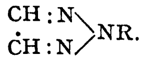
The hypothetical nucleus of **Selenazole,**

$\left.\begin{matrix}N{=}CH\\|\\CH{=}CH\end{matrix}\right\rangle Se$, corresponds to thiazole. Some derivatives of it have been obtained in a manner similar to that used with the analogous thiazole derivatives. **2-Methyl selenazoline,**

$\left.\begin{matrix}N{=}C(CH_3)\\|\\CH_2{-}CH_2\end{matrix}\right\rangle Se$, boiling at 161°, results on treating di-acetamidoethyldiselenide, $(CH_3.CO.NH.CH_2.CH_2Se)_2$, with phosphorus pentachloride. It is an oil with an odour resembling that of pyridine (B. **25,** 3048). **2-Imidotetrahydroselenazole,** *Ethylene-ψ-selenurea,*

$\left.\begin{matrix}NH{-}C(NH)\\|\\CH_2{-}CH_2\end{matrix}\right\rangle Se$, is an oil. It is obtained from bromethylamine and potassium selenocyanide (B. **23,** 1003).

The following four groups of pyrro-diazoles or triazoles can be divided into two families: (1) groups with adjacent N-members; (2) groups with divided N-members. The root-bodies of the pyrro-[*aa*₁]- and [*ab*]-diazoles on the one hand, and the pyrro-[*ab*₁]- and [*bb*₁]-diazoles on the other seem to coincide. They can be distinguished as *v*- (adjacent) triazole and *s*- (symmetrical) triazole, and we may represent their faculty of *desmotropy* by the following formula (compare C. 1902, I. 426; B. **35,** 1038):

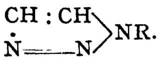
v-Triazole:

$\left.\begin{matrix}CH{-}N\\|\ \ H\\CH{-}N\end{matrix}\right\rangle N.$

s-Triazole:

$\left.\begin{matrix}N{-}CH\\|\ \ H\\N{-}CH\end{matrix}\right\rangle N.$

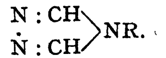
The same uncertainty attaches to those derivatives which are only substituted at the C-atoms. On the other hand, we may distinguish with certainty the four groups indicated by theory in their *N*-alkyl and *N*-aryl derivatives:


$\left.\begin{matrix}CH:N\\\dot{C}H:N\end{matrix}\right\rangle NR.$

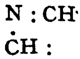
Pyrro[*aa*₁]diazoles.

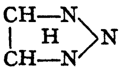
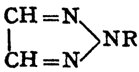

$\left.\begin{matrix}CH:CH\\\dot{N}{=}N\end{matrix}\right\rangle NR.$

Pyrro[*ab*]diazoles.

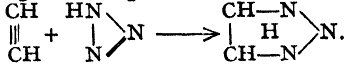

$\left.\begin{matrix}N:CH\\\dot{N}:CH\end{matrix}\right\rangle NR.$

Pyrro[*bb*₁]diazoles.


$\begin{matrix}N:CH\\\dot{C}H:\end{matrix}$

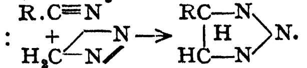
11. **Osotriazoles** or **Pyrro[aa₁]diazoles,**

$\left.\begin{matrix}CH{-}N\\|\ \ H\\CH{-}N\end{matrix}\right\rangle N$ and

$\left.\begin{matrix}CH{=}N\\|\\CH{=}N\end{matrix}\right\rangle NR,$ have been obtained by the following methods:

(1) By the condensation of azoimide with acetylene or α-acetylene carboxylic acids on heating the components in ethereal solution (B. **43,** 2219; C. 1910, II. 225):

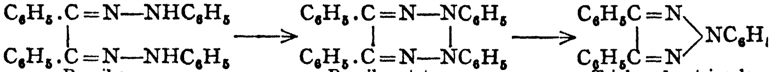


The esters of azoimide combine with acetylene and α-acetylene carboxylic acids to form derivatives of pyrro-[*ab*]diazole.

(2) By the condensation of diazo-methane with some hydrocyanic acid derivatives like ClCN, BrCN, dicyanogen, and cyano-formic acid ester (C. 1907, II. 1491, 1738; 1901, I. 1532):

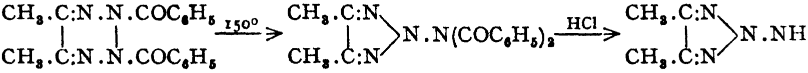


(3) By boiling with acids or distilling the osazones of *o*-diketo-compounds, or the oso-tetrazines, which are the oxidation products of the osazones:

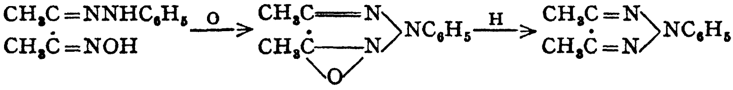


Benzil osazone. Benzil osotetrazone. Triphenylosotriazole.

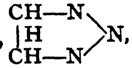
Similarly, *N*-dibenzoylaminoosotriazoles are formed by the transposition of dibenzoylosotetrazines on heating alone or with HCl. The *N*-aminoosotriazoles, treated with nitrous acid, yield osotriazoles with evolution of nitrous oxide (B. **42,** 659; J. pr. Ch. [2], **78,** 544):



(4) From the hydrazoximes of *o*-diketo compounds by removal of H_2O with acetic anhydride or PCl_5. Methylphenylhydrazone oximes of α-diketones also yield osotriazoles with loss of methyl alcohol (Pechmann, A. **262,** 265). On oxidizing the hydrazoximes with N_2O_4 or HgO in chloroform, we obtain endo*xy-dihydro-pyrro*[aa$_1$]-*diazoles,* which easily pass, by reduction or on treating with PCl_5, into the osotriazoles (J. pr. Ch. [2], **57,** 160; C. 1908, II. 1932):



Behaviour.—Osotriazoles are mostly feeble basic liquids with an odour resembling the alkaloids. They distil without decomposition. Their imine hydrogen can be replaced by metals. The phenyl group of the *N*-phenyltriazoles can be split off after amination by simple oxidation. Potassium permanganate oxidizes *C*-alkylosotriazoles to osotriazole carboxylic acids. Nevertheless, the osotriazole ring is stable towards most reagents.

Osotriazole, *v*-Triazole,  m.p. 23°, b.p. 204°, hygroscopic. Silver nitrate precipitates a silver salt, $C_2H_2N_3Ag$; benzoyl-chloride gives the easily decomposed benzoyl-*v*-triazole, m.p. 100°–102°. Osotriazole is formed (1) from acetylene and nitro-hydric acid; (2) by heating its carboxylic acid (see below); (3) from *N*-amino-triazole with nitrous acid.

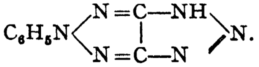
C-**Phenyl-osotriazole,** $C_6H_5.C_2H_2N_2$, m.p. 144°, from its carboxylic acid. *C,C*-**Dimethyl-** and *C,C*-**diphenyl-osotriazole,** m.p. 70° and 138°, from the corresponding *N*-amino-osotriazoles with nitrous acid; the former also by breaking up *N*-phenyl-*C,C*-dimethyl-osotriazole.

N-**Methyl-*C*-chlorosotriazole,** $ClC_2HN_2.CH_3$, b.p.$_{32}$ 63°, and *N*-**methyl-*C*-bromosotriazole,** b.p.$_{39}$ 63°, from diazo-methane and chloro- or bromo-cyanogen. These explode violently above 260° (C. 1907, II. 1738).

N-**Phenyl-osotriazole,** $C_2H_2N_3.C_6H_5$, boiling at 224°, is formed from its carboxylic acid or from glyoxal osotetrazone. *N*-**Phenyl-methyl-osotriazole,** $C_2H(CH_3)N_3.C_6H_5$, boiling at 150° (60 mm.), is obtained from methyl glyoxal. *N*-**Phenyl-dimethyl-osotriazole,** $C_2(CH_3)_2N_3.C_6H_5$, boiling at 190° (60 mm.), is formed from dimethyl glyoxal (I. 349). **Triphenyl-osotriazole,** $C_2(C_6H_5)_3N_3$, melting at 122°, is obtained from benzil (B. **21,** 2806).

N-**Amino-osotriazole,** $C_2H_2N_2.NH_2$, m.p. 51°, *C,C*-**Dimethyl-** and *C,C*-**Diphenyl-*N*-amino-osotriazole,** m.p. 95° and 135°. *N*-**Phenyl-*C*-amino-*C*-methyl-osotriazole,** $C_2(CH_3)(NH_2)N_3C_6H_5$, m.p. 83°, from Pyruamidehydrazone phenylhydrazone, $C_6H_5NHN:C(NH_2).C(CH_3):$-$N.NHC_6H_5$ (B. **26,** 2783; **28,** 1283); it forms a diazo-compound, which, on boiling with water, gives *N*-**phenyl-methyl-hydroxy-osotriazole,** $C_2(CH_3)(OH)N_3C_6H_5$, m.p. 141°, and with potassium-cupric cyanide *N*-phenyl methyl cyano-triazole.

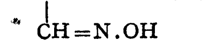
N-**Phenyldiamido-osotriazole,** $C_2N_3(C_6H_5)(NH_2)_2$, melting at 143°, is derived from oxamidephenylhydrazide-amidoxime, $C_6H_5NH.N:$-$C(NH_2)C(NH_2):NOH$. In certain respects it shows great similarity to the aromatic *o*-diamines, in that it forms an *azine*-like blue dyestuff; with *o*-diketones it yields *quinoxaline*-like bodies. It does not form *anhydro*-bases. Nitrous acid converts it into a stable diazo-compound which is readily changed by sodium acetate to *phenylosotriazole-azimide,*



The latter can be readily decomposed into the diazo-compound (A. **295,** 129).

C-**Methyl-, -dimethyl-,** and **-methyl-ethyl-*N*-phenyl** *end***oxy-dihydro-pyrro-[aa₁]-diazole,** m.p. 67°, 93°, and 43° respectively, from the corresponding hydrazoximes with HgO, give by reduction the corresponding osotriazoles, and on heating with halogen hydrides osotriazoles halogenated in the phenyl nucleus (C. 1899, II. 432, etc.).

N-**Phenyltriazole aldehyde,** $C_2H(CHO)N_3C_6H_5$, melting at 70°, is obtained from its *oxime,* melting at 115°, which is formed from di-*iso*nitrosoacetone phenylhydrazone,



$$\begin{array}{l}HON:CH.C{=\!=}N.NHC_6H_5\\ \quad\quad\quad\;\;|\\ \quad\quad\;\;CH=N.OH\end{array}$$

(I. 537). By the exit of water the aldoxime becomes *N-phenylcyanotriazole,* $C(CN)HN_3C_6H_5$, melting at 94°.

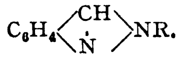
Osotriazole carboxylic acid, $CO_2H.C_3H_2N_3$, m.p. 219° with dec., from propiolic acid and N_3H; also from *N*-phenylosotriazolecarboxylic acid (see below); from *N*-phenyl-pyrro-[*ab*]diazole-*α*- and *β*-carboxylic acid; and from azimido-trichloro-phenol or *bz*-hydroxy-trichloro-benzo-pyrro-[*ab*]-diazole. Its nitrile, m.p. 114°, is formed by the condensation of dicyanogen with diazo-methane.

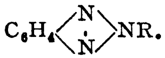
N-**Methylosotriazolecarboxylic acid,** m.p. 142° (C. 1907, II. 1491). *C*-**Phenylosotriazolecarboxylic acid,** m.p. 206° with dec., from phenyl propiolic acid and N_3H.

N-**Phenylosotriazolecarboxylic acid,** $C_2(COOH)HN_3C_6H_5$, m.p. 192°, is obtained by the oxidation of *N*-phenylmethyltriazole; on reduction it splits up into prussic acid and phenyl hydrazido-acetic acid.

Osotriazoledicarboxylic acid, $(CO_2H)_2C_2N_3H$, m.p. 200°, with dec. into CO_2 and oso-triazol. It is formed out of acetylene dicarboxylic acid with N_3H, and by the oxidation of tolutriazole, of *N*-amino-phenyl-pyrro-[*ab*]-diazoledicarboxylic acid and of *C*-**methylosotriazolecarboxylic acid,** m.p. 220° with dec. The esters of these result from boiling aceto-acetic ester diazo-anhydride with alcoholic ammonia (B. **26,** 2736). *N*-**Phenylosotriazoledicarboxylic acid,** $C_2(CO_2H)_2N_3$-C_6H_5, m.p. 236°, from phenyldimethyltriazole, easily gives an anhydride melting at 184°.

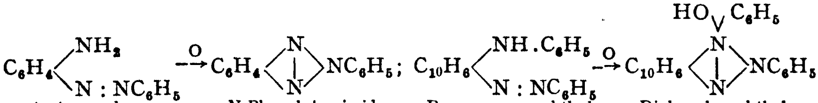
The **pseudo-azimides** may be viewed as benzo-derivatives of oso-triazoles. A constitution similar to that given the indazoles has been ascribed to them, hence they may be called *indodiazoles:*


Indazoles.


Pseudo-azimides.

Pseudo-azimides are produced (1) when *o*-amino-azo-compounds are oxidized (compare B. **25,** 901; **27,** 2374, etc.). The condensation can also be effected by means of thionyl chloride (B. **28,** 2201).

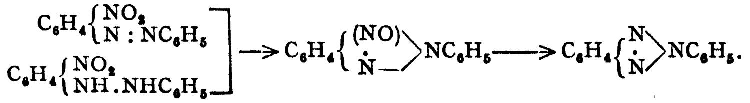
Should the amino-group be substituted, the oxidation will give rise to ammonium hydroxide compounds (B. **20,** 1174; **28,** 328). Heretofore such compounds were only prepared from bases of the naphthalene series. This reaction can easily be made retrogressive by reducing agents:


o-Amino-azobenzene. *N*-Phenyl-ψ-azimido-benzene, m.p. 109°. Benzene-azonaphthyl-aniline. Diphenyl-naphthalene Azoammonium Hydroxide.

o-Anilinonaphthalene-azo-benzoic acid yields the acid of the latter compound. It readily changes to a betaïne-like anhydride,

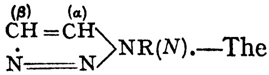
C_6H_5

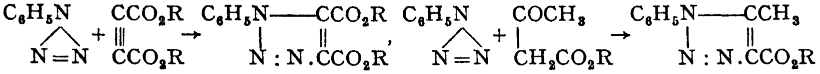
(2) *o*-Nitro-azo-bodies yield, on careful reduction (sodium sulphide and hydrosulphite), first azimido-oxides or azo-nitroso-compounds, which are also formed from *o*-nitro-hydrazo-benzenes by extracting water with glacial acetic acid (J. pr. Ch. [2], **60,** 104; B. **32,** 3266). By reduction with $SnCl_2$ and HCl, these oxides easily pass into azimides (B. **36,** 3822; C. 1903, II. 204):



N-**Phenyl-ψ-azimido-benzene,** $C_6H_4(N_3)C_6H_5$, m.p. 109°; Oxide, $C_6H_4(N_3O)C_6H_5$, m.p. 72°. *N*-**Phenyl-ψ-azimido-toluene,** $CH_3.C_6H_3(N_3)C_6H_5$, m.p. 98°; Oxide, m.p. 142°. *N*,*p*-**Hydroxyphenyl-** and *N*-**Hydroxynaphthyl-azimido-benzene,** m.p. 217°–219° and m.p. 204° (J. pr. Ch. [2], **67,** 580).

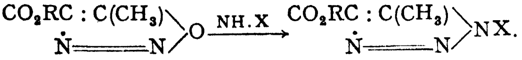
On the breaking up of *N*-phenyl-ψ-azimido-benzene with splitting of the benzo-ring, forming carboxylic acids of the osotriazole series, see J. pr. Ch. [2], **58,** 244.

12. **Pyrro-[ab]-diazoles,**  $\overset{(\beta)}{CH}=\overset{(\alpha)}{CH}\!\!>\!NR(N)$ / $\dot{N}=\!=\!=N$.—The fundamental substance of this group, pyrro-[*ab*]-diazole, cannot be distinguished from osotriazole or *v*-triazole, any more than the compounds of both groups containing a free imino-group. N-substituted pyrro-[*ab*]-diazoles have been obtained by the following methods: (1) Action of phenylazoimide and other esters of azoimide upon α-acetylene carboxylic ester alone, or upon β-ketonic acid ester with sodium alcoholate:

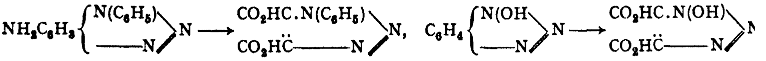


Phenylazoimide also unites with malonic, cyanacetic, and phenyl acetic esters, with benzyl cyanide, and even with acetic and propionic acid esters and with ketones to form hydroxy- and amino-pyrro-[*ab*]-diazoles (B. **35,** 4041; **39,** 3920).

(2) The action of NH_3, hydrazines, semicarbazide, or hydroxylamine upon furo[*ab*]diazoles (*diazo-anhydrides*) produces pyrro-[*ab*]-diazoles (A. **325,** 152; B. **36,** 3612):



(3) From amino compounds substituted on the nitrogen, or benzo-pyrro-[*ab*]-diazoles, pyrro-[*ab*]-diazole carboxylic acids are formed by the breaking up of the benzo-ring (A. **311,** 276; **313,** 251):

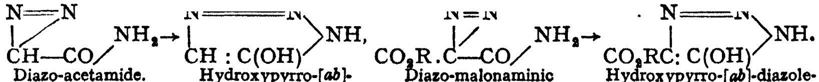


N-**Phenyl-pyrro[ab]-diazole,** $C_2H_2N_3(C_6H_5)$, m.p. 56°, from acetylene and phenylazoimide. *N*-**Phenyl-α-methyl-pyrro-[ab]-diazole,** m.p. 64°, *N*,α-**Diphenyl-pyrro-[ab]-diazole,** m.p. 114°, are easily obtained from their carboxylic acids by heating.

N-**Methyl-α-chloropyrro-[ab]-diazole,** $ClC_2HN_3(CH_3)$, liquid, and *N*-**phenyl-α-chloro-pyrro-[ab]-diazole,** m.p. 50°, result from the α-hydroxy-pyrro-diazolecarboxylic acid esters by treatment with PCl_5, saponification, and elimination of CO_2; the Cl-atom is very mobile.

Carboxylic Acids.—*N*-**Phenyl-α-methyl-pyrro-[ab]-diazolecarboxylic acid,** $(CH_3)(CO_2H)C_2N_3(C_6H_5)$, m.p. 148°, from phenylazoimide and aceto-acetic ester, gives on heating phenyl-methyl-pyrro-diazole, and on subsequent oxidation *N*-**phenyl-pyrro-[ab]-diazole-α-carboxylic acid,** m.p. 176° with dec.; the *N*-**phenyl-pyrro-[ab]-diazoledicarboxylic acid,** m.p. 150°, produced by the oxidation of phenylmethylpyrro-diazole carboxylic acid, or from acetylene dicarboxylic acid ester, or by oxidizing *N*-phenylazimido-aminobenzene, yields, after brief heating, ***N*-phenylpyrro-[ab]-diazole-β-carboxylic acid,** m.p. 151°.

Hydroxypyrro-[ab]*-diazoles.*—These are closely related to the diazo-carboxylic amides, from which they are generated by the action of alkalies, some of them on simply fusing them or on warming their solutions:



Diazo-acetamide. Hydroxypyrro-[*ab*]-diazole. Diazo-malonaminic acid ester. Hydroxypyrro-[*ab*]-diazole-carboxylic ester.

This peculiar transposition is reversible, since, on fusion, or on warming their solutions, the α-oxypyrrodiazoles are converted, more or less completely, into the diazo-carboxylic amides, or their disintegration products. The facility and speed of this isomerization depend upon the substituents. It takes place easily in the case of the hydroxy-pyrrodiazole carboxylic esters, and especially its *N*-aryl substitution products (A. **373,** 336).

The hydroxypyrro-[*ab*]-diazoles are strongly acid compounds. With diazonium salts they couple to form oxy-azo-dyes. With nitrous acid they yield nitroso-hydroxy-pyrro-diazoles, which are possibly oximino-pyrro-diazolones.

α-Hydroxypyrro-[ab]-diazole, $(HO)C_2H_2N_3$, m.p. 130° with dec., from diazo-acetamide, on gentle heating with alkalies, and from its carboxylic ester by saponification and rejection of CO_2. Stable towards alkalies, it is split up on boiling with acids into nitrogen, ammonia, and glycollic acid, probably by way of the diazo-acetamide (B. **43,** 2441). ***N*-Phenyl-α-hydroxypyrrol-[ab]-diazole,** $(HO)C_2HN_3(C_6H_5)$, m.p. 119°, from phenylazoimide and acetic ester, and from its carboxylic acid (see below), on merely warming with water. $KMnO_4$ oxidizes it to oxanilic acid, $C_6H_5NH.COCOOH$. With nitrous acid it yields the yellow unstable N-*phenyloximino-pyrro-*[ab]*-diazolone,* decomposing at 195°, some of the salts of which have various coloured modifications. The transposition of N-*phenyl-benzoyl-oximino-pyrro-diazolone,* m.p. 133°, into N-*phenyl tetrazole carboxylic acid,* is worthy of note (B. **41,** 4055) (see p. 146).

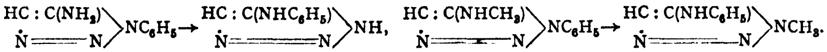
***N*-Phenyl-α-hydroxy-β-methylpyrro-[ab]-diazole,** from methyl malonic ester, α-methylaceto-acetic ester, or propionic acid ester, with $C_6H_5N_3$ and sodium alcoholate, is broken up by $KMnO_4$ into pyro-racemic acid anilide, $C_6H_5NH.COCOCH_3$. ***N*,β-Diphenyl-α-hydroxy-pyrro-[ab]-diazole,** m.p. 151°, from diazo-benzolimide and phenylacetic ester.

α-Hydroxypyrro-[ab]-diazole-carboxylic methyl ester (see above), m.p. 143°, is obtained by the breaking up of *N*-dinitrophenyl-α-hydroxy-pyrro-diazole carboxylic ester on heating with alc. ammonia. On fusing or boiling with alcohol it partly transforms itself into diazo-malonaminic acid ester, from which it can be regenerated by treating with sodium ethylate.

α-Hydroxypyrro-[ab]-diazolecarboxylic acid amide, m.p. 196°, from phenylazoimide and malonamide with elimination of aniline. On fusion it passes into diazo-malonamide, $N_2C(CONH_2)_2$. ***N*-Methyl-** and

N-**phenyl-*α*-oxypyrro-[ab]-diazolecarboxylic methyl ester,** m.p. 136° and 74°, from methyl azide or from phenylazoimide and malonic ester.

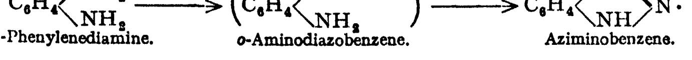
C-**Amino-pyrro-[ab]-diazoles** have been obtained by the condensation of diazo-benzolimide with cyanacetic ester, and benzyl cyanide; also from the chloro-pyrrodiazoles, with ammonia and amines. The amino-pyrro-diazoles not substituted at the nitrogen possess an acid character. With nitrous acid they yield normal diazo-compounds capable of coupling. The *α*-amino-pyrro-diazoles, like the *α*-hydroxy-pyrro-diazoles, are distinguished by remarkable transformation processes. Thus, *N*-**phenyl-*α*-amino-pyrro-[ab]-diazole,** m.p. 110°, obtained from *N*-phenyl-chloro-pyrro-diazole with NH_3, transposes, on fusion, into the isomeric **α-anilino-pyrro-diazole,** m.p. 139°. Similarly, *N*-**phenyl-*α*-methyl-amino-pyrro-[ab]-diazole,** m.p. 102°, on boiling with pyridine, passes into *N*-**methyl-*α*-anilino-pyrro-[ab]-diazole,** m.p. 172°, the methylamino· and anilino-groups changing places:



While these transpositions are not reversible, *Nβ*-**diphenyl-*α*-amino-pyrro-[ab]-diazole,** m.p. 179° (from phenylazoimide and benzyl-cyanide), and **β-phenyl-α-anilino-pyrro-diazole,** m.p. 167°, can be converted into each other, up to a certain condition of equilibrium, by fusion or boiling with pyridine. The same applies to *N*-**phenyl-*α*-amino-pyrro-[ab]-diazolecarboxylic ethyl ester,** m.p. 126°, and *α*-**anilino-pyrro-diazolecarboxylic ethyl ester,** m.p. 130°. The corresponding acids, m.p. 142° and 153°, yield the same *α*-anilino-pyrro-diazole on fusion, with rejection of CO_2 (A. **364,** 183).

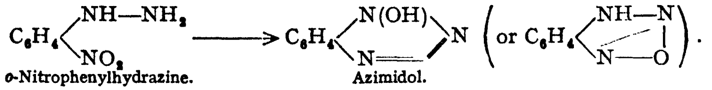
N-**Amino-** and *N*-**oxypyrro-[ab]-diazoles.**—*N*-**Amino-*α*-methyl-pyrro-[ab]-diazole,** $(CH_3)C_2HN_3(NH_2)$, m.p. 70°, from its carboxylic acid, which is obtained by saponifying the condensation product of aceto-acetic ester diazo-anhydride with semi-carbazide (B. **36,** 3612). *N*-**Anilino-*α*-methyltriazole** and its carboxylic acid result from aceto-acetic ester diazo-anhydride with phenylhydrazine, etc. (A. **325,** 156). *N*-**Oxy-*α*-methyl pyrro-[ab]-diazolecarboxylic acid,** decomposing at 205°, is a dibasic acid. Its esters result from aceto-acetic ester diazo-anhydride with hydroxylamine; on oxidation it yields *N*-**hydroxy-pyrro-[ab]-diazoledicarboxylic acid,** $(COOH)_2C_2N_3(OH) + 2H_2O$, which has also been obtained by oxidation of benzazimidole (A. **325,** 162).

Benzopyrro[ab]diazoles or **aziminobenzenes** result from the action of nitrous acid upon *o*-diamines:



o-Phenylenediamine. *o*-Aminodiazobenzene. Aziminobenzene.

When the benzene nucleus is substituted the *N*-substituted azimidobenzols occur in two isomeric forms, determined by the position of the NR-group with reference to the benzene substituents. This is a proof of the unsymmetrical structure of the azimidobenzenes. When, however, the NH-group is free there always appears to be but one preferred position of the hydrogen atom (see uramidoaziminobenzoic acids, A. **291,** 313). The aziminobenzenes no longer manifest the instability of the diazo- or diazoamino-derivatives, but can be distilled without decomposition. The imine hydrogen can be replaced by alkyls. The tertiary bases form ammonium bases with alkyl iodides. N-*Hydroxy-derivatives* of the azimino-benzenes, the **Azimidols,** are formed when alkalies act upon *o*-nitrophenylhydrazines (B. **27,** 3381; **29,** R. 790):



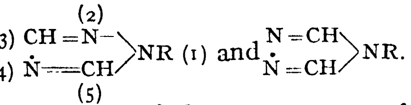
o-Nitrophenylhydrazine. Azimidol.

Azimido-benzene, $C_6H_4(N_3H)$, melting at 98°, is isomeric with phenyl-azoimide. [2]*N*-**Phenylazimido**[4]**ethoxy-benzene** melts at 108°. [2]*N*-**Phenylazimido**[5]**ethoxy-benzene** melts at 99° (compare J. pr. Ch. [2], **53,** 97). *N*-**Tolylazimido-toluene,** $C_7H_6(N_3.C_7H_7)$, melting at 95°, is derived from *o*-aminoditolylamine (B. **25,** 1023), and is isomeric with N-*tolyl-ψ-azimido-toluene,* melting at 126°.

Benzoazimidol, $C_6H_4(N_3OH)$, melting at 157°, is formed in the action of alkalies upon *o*-nitrophenylhydrazine. It is a rather strong acid. It yields the iodethylate of *N*-ethylaziminobenzene with ethyl iodide. Hydriodic acid reduces it to aziminobenzene, while potassium permanganate oxidizes it to a strong tribasic acid, probably *N*-oxy-pyrro-[*ab*]-diazoledicarboxylic acid (see above).

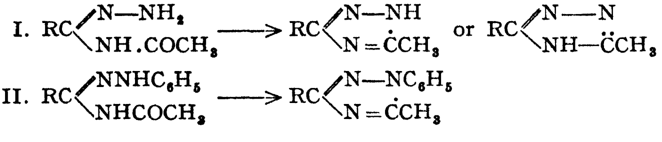
13. *SYM*-TRIAZOLES.

Pyrro-[ab$_1$]-and-[bb$_1$]-diazoles:



In the case of the fundamental substances of these two groups of pyrro-diazoles and the derivatives with unsubstituted imino-group their derivation is uncertain. But the *N*-phenylated derivatives can be allocated to one or other group of pyrro-diazoles from their syntheses.

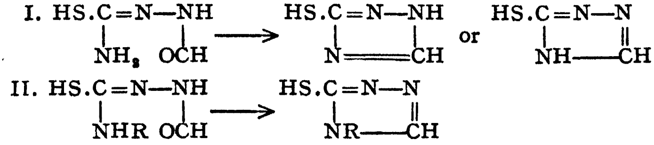
Formation.—(1) Hydrazidines or amidrazones, $RC\left\langle{}^{NNH_2}_{NH_2}\right.$ give, with carboxylic acid anhydrides, acidyl derivatives, which form triazoles by rejection of water:



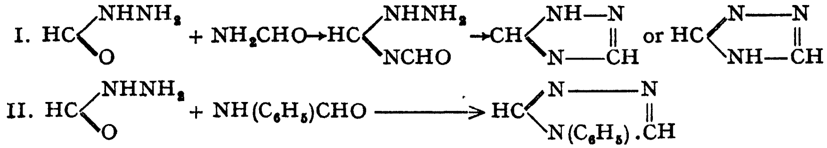
The hydrazines also react similarly with aldehydes and ketones.

(*a*) Thus, triazoles were first produced by Bladin from acid derivatives of dicyano-phenyl-hydrazine, $CN.C(NH_2):NNHC_6H_5$ (B. **18,** 1544; **25,** 183). Similar condensations are shown by *Amido-guanidine,* $NH_2C\left\langle{}^{NNH_2}_{NH_2}\right.$, *Pyruvic hydrazidine,* $CH_3COC\left\langle{}^{NNHC_6H_5}_{NH_2}\right.$, etc. (B. **26,** 2598, 2782; **27,** 989, 3273; A. **303,** 33).

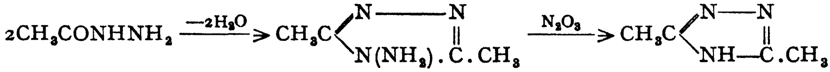
(*b*) Acidylthiosemicarbazides of the formula $HS.C(NH_2):N.$-NHCOR, when heated beyond their melting point, yield mercapto-triazoles, which change to triazoles upon oxidation (B. **29,** 2483; C. 1904, II. 1505):



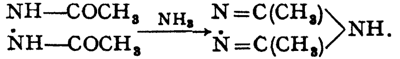
(*c*) On heating *acid amides* with *acid hydrazides*, or, more simply, amides (2 mols.) with hydrazine hydrochloride (1 mol.), triazoles are formed, probably also by way of acid hydrazidines (B. **27,** R. 801; Gaz. chim. ital. **26,** II. 413):



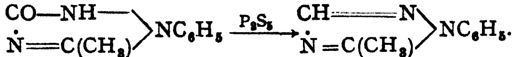
Similarly, *N*-amino-triazoles are formed by heating mono- and diacyl hydrazines alone, and under the action of HNO_2 they split off nitrous oxide and pass into triazoles, probably pyrro-[bb_1]-diazoles:



(2) This group of syntheses is related to the formation of triazoles (probably pyrro-[bb_1]-diazoles) from sym-*diacidyl-hydrazines* by means of zinc ammonium chloride; compare the analogous syntheses of furo- and thio-[bb_1]-diazoles and the scheme of azole syntheses (B. **32,** 797):



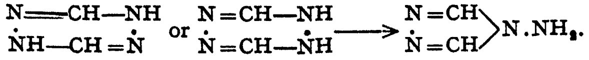
(3) Triazoles are formed from triazolones and urazoles by distillation with P_2S_5, sulphuretted triazoles being formed intermediately (B. **25,** 225; **27,** R. 408; C. 1899, I. 617):



Phenyl-methyl-triazolone. Phenyl-methyl-triazole.

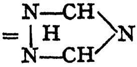
Triazolones with PCl_5 give chloro-triazoles, which reduce to triazoles.

(4) Finally, *N*-aminotriazoles are formed by the transposition of *N*-dihydro-tetrazines:



In the case of *N*-dihydro-tetrazine itself, this transposition takes place on mere fusion, in other cases on heating with aqueous or alcoholic HCl, or conc. alkalies (compare the analogous transposition of dibenzoylosotetrazines into *N*-dibenzoylaminoosotriazoles).

Behaviour.—The triazoles, like the other pyrrodiazoles, are feebly basic, nearly neutral bodies. The **platinum chloride double salts** behave similarly to the pyrazoles (Gaz. chim. ital. **26,** II. 417). The imine-hydrogen is replaceable by metals. *C*-Alkyltriazoles yield triazole carboxylic acids when they are oxidized. In the *N*-phenyltriazoles the phenyl group, particularly after amidation, is split off by oxidation.

sym-**Triazole,** $C_2H_3N_3$ =  $\left.\begin{array}{l} N—CH \\ |\ H \\ N—CH \end{array}\right\rangle N$, m.p. 121°, b.p. 260°, is a feeble base. Its platinum double salt, $(C_2H_3N_3.HCl)_2PtCl_4$, loses 2HCl on heating. Its nitrate melts at 138°; its copper salt, $(C_2H_2N_3)_2Cu$, is obtained from triazole solution with copper sulphate. The sym-triazole results (1) from formamide and formhydrazide; (2) from urazole with P_2S_5; (3) from *N*-amino-triazole with N_2O_3; (4) from its carboxylic acid (A. **303,** 55); (5) from mercaptotriazole by oxidation with H_2O_2 (B. **29,** 2485); (6) from *N*-phenylpyrro-[bb_1]-diazole, or from *N*-phenyl-pyrro-[ab_1]-diazole by oxidative elimination of the phenyl groups (C. 1902, I. 426).

C-**Methyltriazole,** m.p. 94°, from 1-phenyl-3-methylpyrro-[ab_1]-diazole by removal of the C_6H_5 group (B. **25,** 225).

C-**Phenyltriazole,** m.p. 116°, by reduction of *N*-phenyl-bromo-triazole with Na amalgam (B. **43,** 1315). *C*-**Dimethyltriazole,** m.p. 192°, b.p.$_{19}$ 159°; *C*-**diethyltriazole,** m.p. 66°, b.p. 267°; *C*-**diphenyltriazole,** m.p. 192°, and *C*-**difuryltriazole** $(C_4H_3O)_2C_2N_3H$, m.p. 185°, have been obtained by methods (1*a*) and (2), and also from the corresponding *N*-amino-triazoles. The *C*-diphenyltriazole is also formed by the action of acids upon benzal-benzo-hydrazide oxime, $C_6H_5C(:NOH)NH.N:$-CHC_6H_5 (B. **42,** 4200), and from *C*-phenyltetrazole by heating.

Pyrro-[bb$_1$]-diazoles.—*N*-**Phenyl-pyrro-[bb$_1$]-diazole,** m.p. 121°, from formhydrazide and formanilide, has a physiological action similar to that of strychnine (C. 1901, II. 125). *N*-**Methylpyrro-[bb$_1$]-diazole,** m.p. 121°, from formhydrazide and methylformamide and from its mercaptan with H_2O_2. *N*,*C*-**Diphenylpyrro-[bb$_1$]-diazole,** m.p. 142°, from its mercaptan (B. **29,** 2919). **Triphenylpyrro-[bb$_1$]-diazole,** m.p. 292°, from dibenzo-hydrazide chloride and aniline.

Pyrro-[ab$_1$]-diazoles.—*N*-**Methylpyrro-[ab$_1$]-diazole,** m.p. 20°, b.p. 183°, from sodium *sym*-triazole and methyl iodide, as well as formyl-methyl-hydrazide and formamide (C. 1905, II. 490). 1(**n**)-**Phenylpyrro-[ab$_1$]-diazole,** m.p. 47°, b.p. 266°, from its carboxylic acid. 1(*N*)5-**Phenylmethyltriazole,** m.p. 191°, from its carboxylic acid. 1(*N*)3-**Phenylmethyltriazole,** m.p. 87°, b.p. 274°, from phenyl-methyl-triazolone with P_2S_5 (on its formation from phenyl-azo-acetaldoxime-*N*-methyl-ether by elimination of H_2O (see B. **35,** 752). 1(*N*)3-**Diphenyl triazole,** m.p. 97°, from formylbenzamide, $C_6H_5CONH.CHO$, and phenylhydrazine (A. **343,** 229). 1(*N*)5-**Diphenyltriazole,** m.p. 91°, from 1,5-diphenyl-3-chlorotriazole with hydriodic acid and phosphorus. 1(*N*)3,5-**Triphenyltriazole,** m.p. 104°, from benzonitrile (2 mol.), phenyl hydrazine (1 mol.), and sodium; this reaction probably implies the intermediate formation of a hydrazidine, $C_6H_5C(NH)N(C_6H_5).N:C(NH_2)$-$C_6H_5$; substituted phenylhydrazines and benzonitrile probably react in the same manner (J. pr. Ch. [2], **67,** 481).

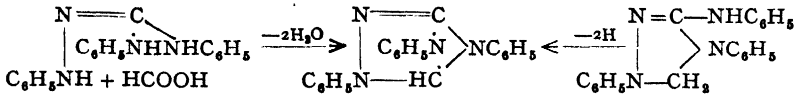
Halogen triazoles are formed from the triazolones by heating with PCl_5 and $POCl_3$ to rather higher temperatures; and from the diazo-compounds of the amino-triazoles with hydro-halogen acids; the halogen is bound up in them as firmly as in chlorobenzene, and can only be extracted by heating with HI + P. **C-Chloro-, C-bromo-,** and **C-iodo-triazole,** $C_2(Hlg)H_2N_3$, m.p. 167°, 189°, and 208° respectively; and **C-methylchlorotriazole,** $C(CH_3)ClN_3H$, m.p. 147°, from the diazo-compounds of the corresponding amino-triazoles (A. **343,** 9). **1-Phenyl-5-chlorotriazole,** m.p. 54°. **1,5-Diphenyl-3-chlorotriazole,** m.p. 96°. **1-Phenyl-3,5-dichlorotriazole,** m.p. 94° (B. **29,** 2671; C. 1897, I. 857).

Hydroxytriazoles (see below: triazolones).

Mercapto-triazoles, from acidyl thiosemicarbazides (method 2) easily yield disulphides on slight oxidation, and triazoles on stronger oxidation, with rejection of sulphur. **Mercapto-triazole,** m.p. 216°; **N-methyl-** and **N-ethylmercaptopyrro-[bb$_1$]-diazole,** m.p. 168° and 97° (B. **29,** 2484; C. 1904, II. 1505).

C-*Amino-triazoles* are obtained synthetically from acid derivatives of amino-guanidine, $NH_2C(:NH)NHNHCOR$. They furnish diazo-compounds, which couple with amines and phenols to form dyestuffs. On reduction these form triazylhydrazines, on oxidation azo-triazoles, and, with hydro-halogen acid, they form halogen-triazoles (A. **343,** 1). **Aminotriazole,** $C_2(NH_2)H_2N_3$, m.p. 159°, from formylamino-guanidine, and from amino-triazole carboxylic acid; **Aminomethyltriazole,** $C_2(CH_3)(NH_2)N_3H$, m.p. 148° (A. **303,** 33). **Amino-N-phenyltriazole,** m.p. 150° (see C. 1899, I. 880).

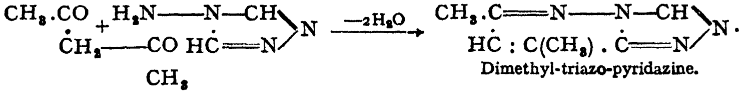
Anilino-N-phenyltriazole, $C_2H(NHC_6H_5)N_3C_6H_5$, m.p. 213°, is formed from aminodiphenylguanidine with formic acid (B. **33,** 1067). **1,4-Diphenyl-3-anilinodihydrotriazole** (see below), m.p. 128°, from triphenylguanidine and formaldehyde, as well as its homologues, split off two H-atoms on gentle oxidation and pass into di-cyclic so-called *end*imino-dihydro-triazoles, which are also obtained direct by the condensation of triaryl-guanidines with carboxylic acids or their chlorides:



The *end*imino-dihydro-triazoles are yellow compounds with strong basic properties, easily split up by caustic alkalies with regeneration of the components (B. **38,** 856, 4049). The nitrates of the *end*imino-dihydro-triazoles are particularly insoluble; the **1,4-diphenyl-*end*anilinodihydrotriazole,** m.p. 189°, named *nitron,* has been specially recommended for the qualitative and gravimetric estimation of nitric acid (B. **38,** 861).

Correspondingly, end*oxy-* and endo*thio-dihydro-triazoles* have been obtained by the condensation of carboxylic acids and their chlorides with diaryl semi-carbazides and diaryl-thio-semi-carbazides (J. pr. Ch. [2], **67,** 201).

N-*Aminotriazoles* (N-*aminopyrro*-[bb$_1$]-*diazoles*) are formed on heating mono-and diacyl-hydrazines, or by transposition of N-dihydro-tetrazines. **N-Amino-triazole,** $C_2H_2N_3(NH_2)$, m.p. 83°, is formed on heating formyl hydrazine to 210°–220°; or by melting N-dihydro-tetrazine and its carboxylic acids; or from *N*-aminotriazole dicarboxylic acid (see below) (B. **41,** 3168). ***N*-Aminodimethyl-, -diethyl-,** and **-diphenyl-triazole,** m.p. 199°, 167°, and 258° respectively. The first of these is also formed from aceto-hydroxamic acid chloride and hydrazine (B. **40,** 1677). The *N*-amino-triazoles, treated with nitric acid, split off nitrous oxide and yield triazoles. With aldehydes and ketones they condense like substituted hydrazines, with rejection of water: **benzylidene-*N*-amino-triazole,** $C_6H_5CH:N.N_3C_2H_2$, m.p. 170°; 1,3-diketones and β-ketonic acid esters form dicyclic compounds containing a combined triazole and pyridazine ring (B. **42,** 2594):

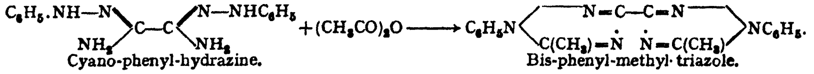


Dimethyl-triazo-pyridazine.

Triazole Carboxylic Acids.—**Triazole-3-carboxylic acid,** $C_2H_2(COOH)N_3$, melts with decomposition at 137°. It is produced in the oxidation of methyltriazole and when $KMnO_4$ acts upon *N*-aminophenyltriazole carboxylic acid. ***N*-Phenyltriazole-3-carboxylic acid,** $C_2H(COOH)N_3.C_6H_5$, melting at 184°, is derived from phenylmethyltriazole as well as by the exit of CO_2 from ***N*-phenyltriazole-3,5-dicarboxylic acid,** $C_2(COOH)_2N_3.C_6H_5$, which is prepared by the oxidation of ***N*-phenyl-5-methyltriazole-3-carboxylic acid,** $C_3(CH_3)(COOH)N_3.C_6H_5$, melting at 177°. The latter results from the saponification of its nitrile, as well as by the moderated oxidation of acetylphenylmethyl triazole.

***C*-Aminotriazolecarboxylic acid,** $C_2(NH_2)(COOH)N_3H$, m.p. 182°, with rejection of CO_2, is formed from oxalyl-amino-guanidine; also, with ***N*-aminotriazoledicarboxylic acid,** $C_2(CO_2H)_2N_3(NH_2)+H_2O$, m.p. 77° with dec., by heating *N*-dihydro-tetrazinedicarboxylic acid (see below) with conc. potash. It yields a diazo-triazolecarboxylic acid which, on heating with alcohol, yields triazole (A. **303,** 51; B. **40,** 1194).

Bistriazoles are obtained from cyano-hydrazine and phenyl-hydrazine (B. **26,** 2389) with acids or their anhydrides (B. **21,** 3063; **30,** 1194):

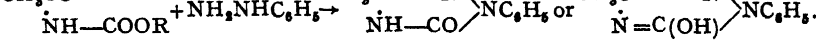


Cyano-phenyl-hydrazine. Bis-phenyl-methyl-triazole.

Bistriazole, $(C_2H_2N_3)_2$, from cyano-hydrazine and formic acid, sublimes above 300°.

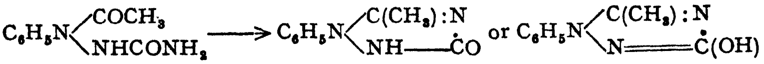
Triazolones, *keto-derivatives of dihydro-triazoles,* which also react in tautomeric form as hydroxy-triazoles (compare pyrazolone above, and C. 1897, II. 269), are formed:

(1) From acetyl urethane with phenylhydrazines (Andreocci, B. **22,** R. 737):



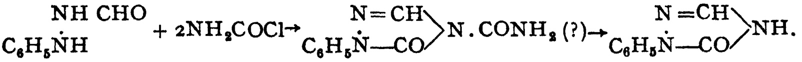
This reaction recalls the formation of phenylmethylpyrazolone from aceto-acetic ester and phenylhydrazine.

(2) Isomeric 1,3-triazolones are formed from acid derivatives of phenylsemicarbazide by heating with dilute alkali (B. **29,** 1946; **31,** 378):



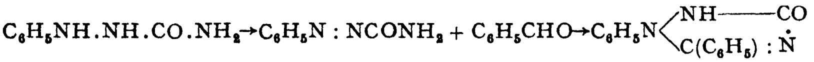
$$C_6H_5N\left\langle\begin{array}{l}COCH_3\\NHCONH_2\end{array}\right. \longrightarrow C_6H_5N\left\langle\begin{array}{l}C(CH_3):N\\NH\text{——}\dot{C}O\end{array}\right. \text{ or } C_6H_5N\left\langle\begin{array}{l}C(CH_3):N\\N\text{=====}\dot{C}(OH)\end{array}\right.,$$

(3) By the action of *sym*-acidyl-phenyl-hydrazines upon carbaminic acid chloride, carbaminic acid derivatives of triazolones, or hydroxytriazolones, are formed, from which the latter are obtained by saponification. The reaction fails in benzoylphenylhydrazine, but recurs in hexahydrobenzoylphenylhydrazine (B. **36,** 1092):



$$\begin{array}{l}NH\ CHO\\C_6H_5\dot{N}H\end{array} + 2NH_2COCl \rightarrow \begin{array}{l}N{=}CH\\C_6H_5\dot{N}\text{—}CO\end{array}\!\!\Big\rangle N.CONH_2\,(?) \rightarrow \begin{array}{l}N{=}CH\\C_6H_5\dot{N}\text{—}CO\end{array}\!\!\Big\rangle NH.$$

(4) Triazolones are also formed, by condensing aldehydes with semicarbazides, in the presence of oxidizing agents, or with phenylazocarbamides or azodicarbonamide (C. 1898, II. 199; 1900, I. 818):

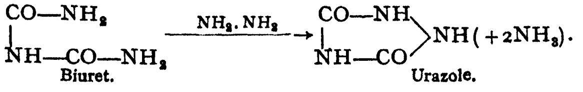


$$C_6H_5NH.NH.CO.NH_2 \rightarrow C_6H_5N:NCONH_2 + C_6H_5CHO \rightarrow C_6H_5N\left\langle\begin{array}{l}NH\text{———}CO\\C(C_6H_5):\dot{N}\end{array}\right.$$

In accordance with their formulation as hydroxytriazoles, the triazolones react mostly as acids; with P_2S_5 they give triazoles, and with PCl_5 chlorotriazoles.

1,3-Triazolone, 1,3-*Hydroxytriazole,* NH.NH.CO.N:CH or NH.N:C(OH).N:CH, m.p. 234°, is obtained from acetone semicarbazone and formic acid, as well as from hydroxytriazole carboxylic acid, resulting from the action of dilute sulphuric acid upon diazotriazole carboxylic acid (B. **31,** 2444). It is an acid. **1-Phenyl-3-triazolone,** from phenyl semicarbazide and formic acid, sublimes and melts at a very high temperature. **1-Phenyl-5-triazolone,** m.p. 183°, is obtained from formylphenylhydrazide with carbaminic acid chloride (see above) or from its carboxylic acid (**1-phenyl-5-triazolone-3-carboxylic acid**), generated on oxidizing **1-phenyl-3-methyl-5-triazolone,** m.p. 167°, b.p. above 300° (B. **24,** R. 203). The latter is also obtained from aceto-phenylhydrazide with $NH_2.COCl$. ***C*-Phenyltriazolone,** $C_6H_5C:N.NH.CO.NH$ or $C_6H_5C:N.CONH.NH$, m.p. 322°, is formed by heating benzal-semi-carbazone with ferric chloride in alcoholic solution (C. 1900, I. 818).

The *urazoles* are the diketo-derivatives of tetrahydrotriazole. They result on heating urea and its derivatives—*e.g.*, allophanic ester, biuret, etc.—with hydrazine salts:

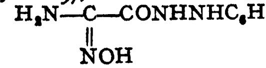


$$\begin{array}{l}CO\text{—}NH_2\\|\\NH\text{—}CO\text{—}NH_2\end{array} \xrightarrow{NH_2.NH_2} \begin{array}{l}CO\text{—}NH\\|\\NH\text{—}CO\end{array}\!\!\Big\rangle NH(+2NH_3).$$

Biuret. Urazole.

Urazole, 3,5-*Diketotriazolidine,* $C_2H_3O_2N_3$, melting at 244°, is obtained from hydrazodicarbonamide, $NH_2.CO.NH.NH.CO.NH_2$ (A. **288,** 16).

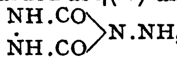
Urazole is a strong monobasic acid. It yields triazole when distilled with P_2S_5. **1-Phenylurazole,** $C_6H_5N—NH—CO—NH—CO$, melting at 263°, is formed from urea and phenylhydrazine, from phenylsemicarbazido-carboxylic ester (B. **28,** 829), as well as from phenylhydrazido-oxalhydroxamic acid,



$H_2N—\underset{\overset{\|}{NOH}}{C}—CONHNHC_6H_5$

, by Beckmann's transformation (A. **295,** 136). Methyl iodide converts it into *dimethylphenylurazole,* melting at 95°. Isomeric 4-**Phenylurazole,** $C_6H_5N—CO—NH—NH—CO$, melting at 203°, is formed by the interaction of hydrazo-dicarbonamide and aniline hydrochloride.

The *urazines,* obtained by the condensation of hydrazine derivatives of carbonic acid, may be regarded as 4(*N*)-amino-urazoles (B. **40,** 2093). 4(*N*)-**Aminourazole,** *Urazine,*

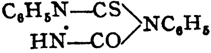


$\begin{matrix}NH.CO\\NH.CO\end{matrix}\!\!>N.NH_2$

, m.p. 270°, also known as *diurea* or *bishydrazidicarbonyl,* is formed from hydrazidicarboxylic ester and hydrazine hydrate at 110°. **1-Phenyl-4-aminourazole,** *phenylurazine,* $C_6H_5N_2HC_2O_2N.NH_2$, m.p. 245°, from phenylhydrazido-dicarboxylic ester acid chloride, $C_6H_5N(COCl)NHCOOR$, and hydrazine; with nitrous acid it yields 1-phenylurazole (B. **38,** 455). **1-Phenyl-4-anilidourazole,** *Diphenylurazine,* $C_6H_5N_2HC_2O_2N.NHC_6H_5$, m.p. 264° (see B. **32,** 16).

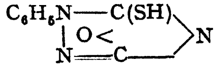
Thio- and imido-derivatives of urazole are obtained from the corresponding thiourea and guanidine derivatives of hydrazine (B. **29,** 2506; **32,** 1081).

Thiourazole, $NH.CO.NH.CS.NH$, m.p. 177°, from hydrazo-thiodicarbonamide, $NH_2CS.NH.NH.CONH_2$. **1-Phenyl-3-thiourazole,** m.p. 195° (B. **36,** 3151). **1,4-Diphenyl-5-thiourazole,** from diphenylthiosemicarbazide and $COCl_2$, in two desmotropic forms,



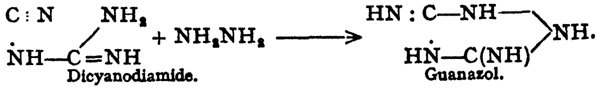
$\begin{matrix}C_6H_5N—CS\\HN—CO\end{matrix}\!\!>NC_6H_5$

, unstable, m.p. 139°, and



$\begin{matrix}C_6H_5N—C(SH)\\ O<\\ N{=}C—\end{matrix}\!\!>NC_6H_5$

, stable, m.p. 220° (B. **42,** 4763). **Dithiourazole,** $NH.CS.NH.CSNH$, m.p. 245° with dec., and **Iminothiourazole,** $NH.CS.NH.C(NH)NH$, m.p. 222°, are formed together by the action of strong hydrochloric acid upon hydrazodithiodicarbamide (B. **29,** 2506). **1-Phenyl-3,5-dithiourazole,** m.p. 181° (B. **37,** 184). **Diiminourazole, Guanazole,** $NH.C(NH).NH.-C(NH).NH$, m.p. 206°, from dicyanodiamide and hydrazine (B. **27,** R. 583):

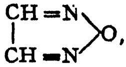


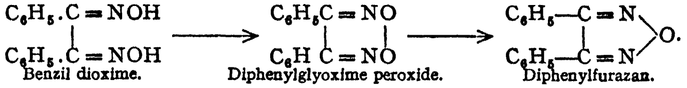
$$\begin{matrix}C:N & NH_2\\ NH—C{=}NH\end{matrix} + NH_2NH_2 \longrightarrow \begin{matrix}HN:C—NH—\\HN—C(NH)\end{matrix}\!\!>NH.$$

Dicyanodiamide. Guanazol.

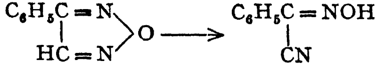
4(*N*)-**Aminoguanazole,** *Guanazine,* m.p. 257° with dec., from hydrazine with two mol. cyanogen bromide (C. 1908, I. 48).

14. FURAZANS OR FURO-$[aa_1]$-DIAZOLES.

The furazans or *azoxazoles, furo-*$[aa_1]$*-diazoles,*  correspond to the osotriazoles. Just as the latter are obtained from the osazones, so furazans are produced from the glyoximes or the dioximes of *o*-diketones by the action of alkalies:



As we observed in connection with the isoxazoles, those furazan derivatives in which the H-atoms of both methine groups are substituted are stable bodies. If one of the groups is free, a rearrangement into nitriles of *a*-ketonic acid oximes may readily take place. The alkyl furazans can be oxidized to furazan carboxylic acids.

Phenylfurazan, $C_2H(C_6H_5)N_2O$, melting at 30°, is very volatile. It is formed when soda acts upon phenylglyoxime diacetate. Sodium hydroxide converts it readily into the oxime of benzoyl cyanide,  (B. **24,** 3503). It is stable towards acids. **Dimethylfurazan,** $C_2(CH_3)_2N_2O$, melting at -7° and boiling at 156°, results when dimethyl glyoxime is heated with ammonia to 160° - 170°. **Methylethylfurazan,** $C_2(CH_3)(C_2H_5)N_2O$, boiling at 170°, is similarly obtained from methylethylglyoxime. **Diphenyl furazan,** $C_2(C_6H_5)_2N_2O$, melting at 94°, rearranges itself by prolonged heating into isomeric dibenzenylazoxime (see below) (A. **264,** 180). **Dibenzoylfurazan,** $C_2(COC_6H_5)_2N_2O$, melting at 118°, is prepared from dibenzoylfuroxan (B. **26,** 529).

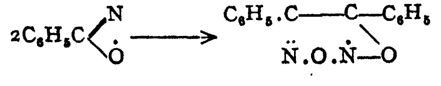
Furazancarboxylic Acid, $C_2H(COOH)N_2O$, melting at 107°, by oxidation of **furazylpropionic acid,** the anhydride of dioximinovaleric acid (I. 546). **Methylfurazancarboxylic acid,** $C_2(CH_3)(COOH)N_2O(+H_2O)$, melting at 74° (39°), and **Furazandicarboxylic acid,** $C_2(COOH)N_2O$, melting at 178° with decomposition, are formed when potassium permanganate acts upon dimethylfurazan. The dicarboxylic, like the monocarboxylic acid, is easily converted by boiling water into cyanimidoacetic acid.

Consult B. **28,** 723, for **oxyfurazan carboxylic acid.**

Benzo-, naphtho-, phenanthro-furazans, etc., have been prepared from the *o*-dioximes of the benzene, naphthalene, and phenanthrene series (see also B. **29,** R. 790).

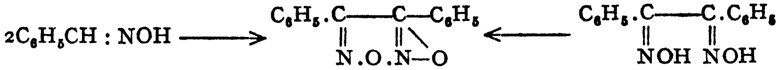
The compounds formerly known as "*glyoxime peroxides*" must, according to later investigations, be regarded as *endo*xy-dihydro-furo-$[aa_1]$-diazoles or *furoxans* (Wieland, A. **358,** 36; **367,** 52, 80; **375,** 297). They are formed:

(1) By the polymerization of nitrile oxide:

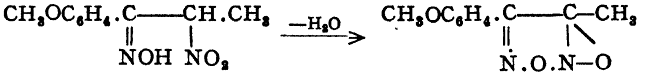


The intermediate formation of nitrile oxides also accounts for the formation of furoxans from hydroxamic acid chlorides and nitrolic acids.

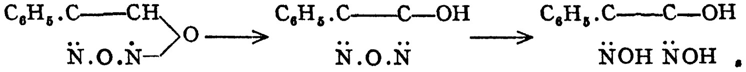
(2) By the oxidation of aldoximes and glyoximes with NO_2 in ether solution (B. **23,** 3496):



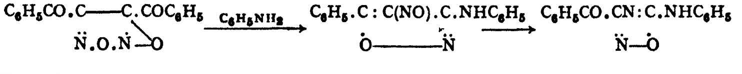
(3) From the mono-molecular *pseudo*-nitrosites (nitrites) of many propenylbenzenes on boiling with alcohol or water (A. **329,** 238):



By reduction with HI or Sn and HCl, or by treating with PCl_5, the furoxans can be reduced to the corresponding furazans. As in the case of the furazans, the disubstituted furoxans are stable compounds, while the mono-substituted ones are easily split up by alkalies. The first product consists of hydroxyfurazans, which are then split up to form the oximes of α-ketone hydroxamic acid:



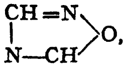
Dimethylfuroxan, $(CH_3)_2C_2N_2O_2$, b.p. 220°. **Phenylfuroxan,** $C_6H_5C_2HN_2O_2$, m.p. 95°, from phenylglyoxime with NO_2, is split up by alkali to form **phenyl-hydroxyfurazan,** m.p. 111° with dec., and then *iso*nitrosophenylacetohydroxamic acid (see above). On boiling with water it decomposes into formohydroxamic acid and benzonitrile oxide, which immediately polymerizes to **diphenylfuroxan.** The latter is also formed from benzaldoxime and benzil-dioxime, or by the spontaneous decomposition of benzonitrilic acid. **Dibenzoylfuroxan** is formed by the action of nitric acid upon acetophenone. With amines there occurs a primary disintegration with subsequent closing of the ring, and rejection of a benzoyl group. This yields strongly coloured nitroso-isoxazoles (formerly called *iso*-triazoxoles), and these, on boiling with alcohol or glacial acetic acid, form colourless azoximes:



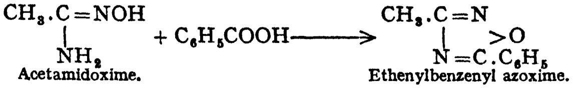
Dichloro,- dibromo-, and **di-iodo-furoxans,** liquid, m.p. 50° and 91° respectively, are formed by the action of halogens upon fulminate of mercury (B. **42,** 4192).

Furoxanmonocarboxylic acid, $(COOH)C_2HN_2O_2$, m.p. 90° with dec., is split up, on merely standing in water, to *iso*nitroso-malonehydroxamic acid. It is formed by saponification and rejection of CO_2 from **furoxandicarboxylic acid ethyl ester,** $(CO_2C_2H_5)_2C_2N_2O_2$, b.p.$_{16}$ 164°, obtained by the action of fuming nitric acid upon aceto-acetic ester with intermediate formation of acetic ester nitrolic acid, $CO_2RC(NO_2):(NOH)$, or from chloroximido-acetic ester by treating with sodium carbonate. **Furoxandicarboxylic acid amide,** m.p. 218° with dec., is closely related to fulminuric acid, $CNCH(NO_2)CONH_2$ (Vol. I.), from which it results by the action of concentrated H_2SO_4, and into which it can be partly converted by boiling in water (A. **367,** 80).

15. AZOXIMES OR FURO[ab₁]DIAZOLES.

The azoximes, *furo*[a,b₁]*diazoles*,  $\begin{matrix} CH=N \\ | \\ N—CH \end{matrix}\!\!>O$, correspond to the triazoles or pyrro[*ab*₁]diazoles, and just as they are obtained from the amidrazones, so the azoximes are prepared:

1. From amidoximes and carboxylic acids (their chlorides or anhydrides):

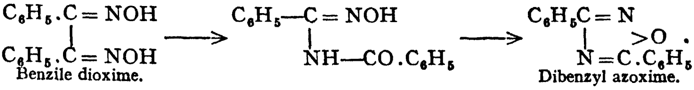


$$\begin{matrix} CH_3.C=NOH \\ | \\ NH_2 \end{matrix} + C_6H_5COOH \longrightarrow \begin{matrix} CH_3.C=N \\ | \quad >O \\ N=C.C_6H_5 \end{matrix}$$

Acetamidoxime. Ethenylbenzenyl azoxime.

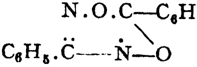
The amidoximes combine with the aldehydes of the fatty series to form *hydrazoximes*, which part readily with hydrogen, and become azoximes. $COCl_2$ and $CSCl_2$ form *carbonylazoximes* (furo[*ab*₁]diazolones) and *azoximthiocarbinols* (B. **19,** 1487; **22,** 2422; **28,** 2231).

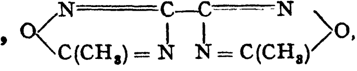
2. Azoximes are also prepared by Beckmann's transformation from glyoximes or furazans (B. **27,** R. 800):

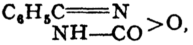


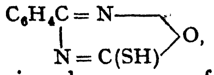
$$\begin{matrix} C_6H_5.C=NOH \\ | \\ C_6H_5.C=NOH \end{matrix} \longrightarrow \begin{matrix} C_6H_5—C=NOH \\ | \\ NH—CO.C_6H_5 \end{matrix} \longrightarrow \begin{matrix} C_6H_5C=N \\ | \quad >O \\ N=C.C_6H_5 \end{matrix}.$$

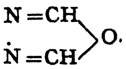
Benzile dioxime. Dibenzyl azoxime.

Diethenyl azoxime, $C_2(CH_3)_2N_2O$ (B. **17,** 2755), is a very volatile body. **Ethenyl benzenyl azoxime,** $C_2(CH_3)(C_6H_5)N_2O$, melts at 41°. **Dibenzenyl azoxime,** $C_2(C_6H_5)_2N_2O$, melting at 108° and boiling at 290°, also results when hydroxylamine acts upon benzoyl benzimide chloride (A. **296,** 284); from the oxidation of benzaldoxime with sodium hypochlorite; and by reduction from dibenzenyl oxo-azoxime,  $\begin{matrix} N.O.C—C_6H_5 \\ C_6H_5.\ddot{C}—\dot{N}—O \end{matrix}$, m.p. 134°, obtained by spontaneous decomposition of benzohydroxamic acid chloride, and by the action of alc. HCl upon tribenzo-nitrile oxide (B. **42,** 806).

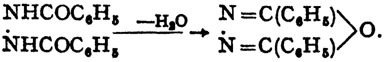
Oxalenebisazoximethenyl,  $O\!\!<\begin{matrix} N=\!=\!=C—C=\!=\!=N \\ \quad | \quad\; | \\ C(CH_3)=N \quad N=C(CH_3) \end{matrix}\!\!>O$, melts at 165° (B. **22,** 2949).

Benzenyl Carbonyl Azoxime,  $\begin{matrix} C_6H_5C=\!=N \\ NH—CO \end{matrix}\!\!>O$, melting at 198°, and

Benzenylazoxime-thiocarbinol,  $\begin{matrix} C_6H_4C=N— \\ | \\ N=C(SH) \end{matrix}\!\!>O$, melting at 131°, are produced from benzenylamidoxime by means of $COCl_2$ and $CSCl_2$.

16. OXYDIAZOLES OR FURO-[bb₁]-DIAZOLES:  $\begin{matrix} N=CH \\ N=CH \end{matrix}\!\!>O$.

Derivatives of the hypothetical oxydiazole or furo-[*bb*₁]-diazole are obtained from *sym*-diacidyl hydrazines on heating alone or with dehydrating agents, as in the formation of furans from 1,4-diketones (B. **32,** 797; J. pr. Ch. [2], **68,** 130):

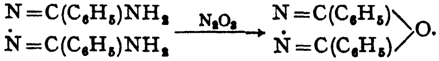

$$\left.\begin{array}{l}\mathrm{NHCOC_6H_5}\\ \dot{\mathrm{N}}\mathrm{HCOC_6H_5}\end{array}\right. \xrightarrow{-\mathrm{H_2O}} \left.\begin{array}{l}\mathrm{N=C(C_6H_5)}\\ \dot{\mathrm{N}}\mathrm{=C(C_6H_5)}\end{array}\right\rangle \mathrm{O}.$$

Dimethyl-oxydiazole, *Dimethylfuro-*[bb$_1$]*-diazole,* $N_2(CCH_3)_2O$, b.p. 179°, is obtained from diacetohydrazide and acetic anhydride or by heating tetracetylhydrazine; alkalies and acids decompose it more easily than the aromatic derivatives. **Diethyl-, Dipropyl-, Di*iso*propyl-, Di*iso*butyl-furo-[bb$_1$]-diazole,** b.p. 198°, 227°, 209°, 232°; **Didecyl-** and **Dipentadecyl-furo-[bb$_1$]-diazole,** m.p. 54°, b.p.$_{22}$ 275°, and m.p. 72°, b.p.$_{15}$ 215° (J. pr. Ch. [2], **69,** 481 *ff.*).

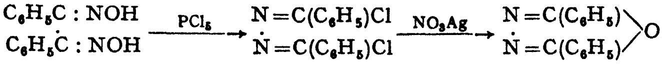
Diphenyl-oxydiazole, *Diphenylfuro-*[bb$_1$]*-diazole, Dibenzylisazoxime,* m.p. 138°, b.p.$_{15}$ 231°, forms with $AgNO_3$ a rather insoluble double compound. It is formed (1) by heating dibenzo-hydrazide (see above).

(2) From silver benzal-benzo-hydrazide and iodine (J. pr. Ch. [2], **70,** 414).

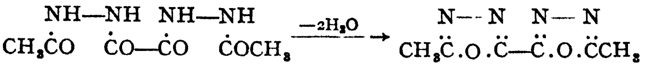
(3) From dibenzenylhydrazidine with N_2O_3 (A. **297,** 264):


$$\left.\begin{array}{l}\mathrm{N=C(C_6H_5)NH_2}\\ \dot{\mathrm{N}}\mathrm{=C(C_6H_5)NH_2}\end{array}\right. \xrightarrow{\mathrm{N_2O_3}} \left.\begin{array}{l}\mathrm{N=C(C_6H_5)}\\ \dot{\mathrm{N}}\mathrm{=C(C_6H_5)}\end{array}\right\rangle \mathrm{O}.$$

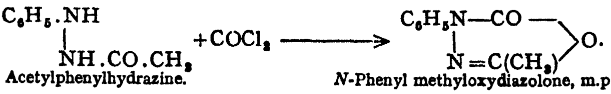
(4) Like the isomeric dibenzenyl azoxime and diphenyl furazan (see below) from benzil dioxime:


$$\left.\begin{array}{l}\mathrm{C_6H_5C:NOH}\\ \mathrm{C_6H_5\dot{C}:NOH}\end{array}\right. \xrightarrow{\mathrm{PCl_5}} \left.\begin{array}{l}\mathrm{N=C(C_6H_5)Cl}\\ \dot{\mathrm{N}}\mathrm{=C(C_6H_5)Cl}\end{array}\right. \xrightarrow{\mathrm{NO_3Ag}} \left.\begin{array}{l}\mathrm{N=C(C_6H_5)}\\ \dot{\mathrm{N}}\mathrm{=C(C_6H_5)}\end{array}\right\rangle \mathrm{O}.$$

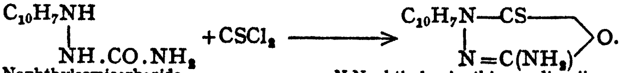
Dimethyl- and **diphenyl-bisfuro-[bb$_1$]-diazole,** m.p. 212° and 270°, have been obtained by heating diacetyl- and dibenzoyl-oxal-hydrazide with P_2O_5 (J. pr. Ch. [2], **70,** 427):


$$\begin{array}{ccc}\mathrm{NH{-}NH} & \mathrm{NH{-}NH} & \\ \mathrm{CH_3\dot{C}O} & \mathrm{\dot{C}O{-}\dot{C}O} & \mathrm{\dot{C}OCH_3}\end{array} \xrightarrow{-2\mathrm{H_2O}} \begin{array}{cc}\mathrm{N{-}N} & \mathrm{N{-}N}\\ \mathrm{CH_3\ddot{C}.O.\ddot{C}{-}} & \mathrm{\ddot{C}.O.\ddot{C}CH_3}\end{array}$$

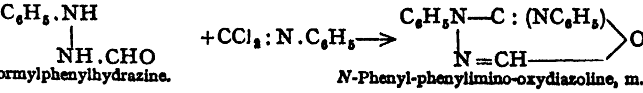
The **Keto-, thio-,** or **imino-oxydiazolines** are derivatives of *dihydro-oxydiazole* or *oxydiazoline.* They are produced from carboxylic and urea derivatives of phenylhydrazine, naphthylhydrazine, etc., through the action of phosgene, $COCl_2$, thiophosgene, $CSCl_2$, and phenyl *iso*cyanide chloride, $CCl_2:NC_6H_5$ (B. **23,** 2843; **24,** 4178; **26,** 2870):

(1)

$$\left.\begin{array}{l}\mathrm{C_6H_5.NH}\\ \quad|\\ \mathrm{NH.CO.CH_3}\end{array}\right. + \mathrm{COCl_2} \longrightarrow \left.\begin{array}{l}\mathrm{C_6H_5N{-}CO{-}}\\ \quad|\\ \mathrm{N=C(CH_3)}\end{array}\right\rangle \mathrm{O}.$$

Acetylphenylhydrazine. *N*-Phenyl methyloxydiazolone, m.p. 280°.

(2)

$$\left.\begin{array}{l}\mathrm{C_{10}H_7NH}\\ \quad|\\ \mathrm{NH.CO.NH_2}\end{array}\right. + \mathrm{CSCl_2} \longrightarrow \left.\begin{array}{l}\mathrm{C_{10}H_7N{-}CS{-}}\\ \quad|\\ \mathrm{N=C(NH_2)}\end{array}\right\rangle \mathrm{O}.$$

Naphthylsemicarbazide. *N*-Naphthylaminothio-oxydiazoline, m.p. 218°.

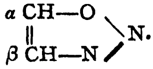
(3)

$$\left.\begin{array}{l}\mathrm{C_6H_5.NH}\\ \quad|\\ \mathrm{NH.CHO}\end{array}\right. + \mathrm{CCl_2:N.C_6H_5} \longrightarrow \left.\begin{array}{l}\mathrm{C_6H_5N{-}C:(NC_6H_5)}\\ \quad|\\ \mathrm{N=CH{-}}\end{array}\right\rangle \mathrm{O}.$$

Formylphenylhydrazine. *N*-Phenyl-phenylimino-oxydiazoline, m.p. 99°.

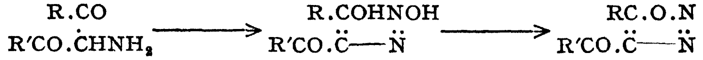
Finally, phenyl-carbazinic acid esters, $C_6H_5NHNH.COOR$, and phenyl thiocarbazinic acid esters, $C_6H_5NHNH.COSR$, treated with $COCl_2$, give alkoxy- and alkylthioloxydiazolones (J. pr. Ch. [2], **60**, 38).

For dihydro-furo-diazoles, see also J. pr. Ch. [2], **67**, 417.

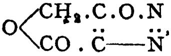
17. FURO-[AB]-DIAZOLE,



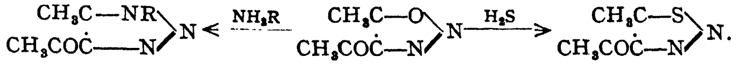
17. The ring of furodiazole is also found in the diazo-anhydrides formed by treating amino-β-diketo-compounds with nitrous acid:



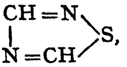
On a different formulation of the diazo-anhydrides, see B. **42**, 2347; A. **373**, 339.

Diazo-acetyl-acetone-anhydride, *α-Methyl-β-acetylfuro*-[ab]-*diazole*, Oil; **Diazo-benzoyl-acetone-anhydride,** *α-Methyl-β-benzoylfuro*-[ab]-*diazole*, m.p. 66°; **Diazo-acetic acid ester anhydride,** *α-Methylfuro*-[ab]-*diazolecarboxylic ester*, b.p.$_{12}$ 102° to 104° (*cf.* Vol. I.); **Diazo-tetronic acid anhydride,**  m.p. 93°.

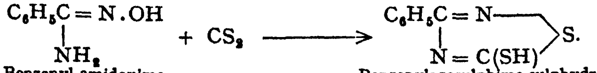
The furo-[*ab*]-diazoles are less stable than the corresponding thio- and pyrro-diazoles. Alkalies split them up with partial formation of diazo-bodies of the type of diazo-methane (diazo-acetic acid, diazo-acetophenone). On boiling with water they undergo separation of N_2 and partial transposition. With NH_3, amines, phenylhydrazine, and hydroxylamine, they undergo intermediate ring division and yield pyrro-[*ab*]-diazoles, and, with H_2S, thio-[*ab*]-diazoles (A. **325**, 129; B. **36**, 3612):



18. THIO-[AB$_1$]-DIAZOLES,

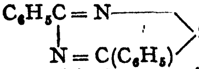


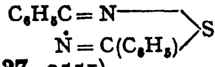
These compounds (*azosulphimes*), result from the action of carbon disulphide upon amidoximes (B. **24**, 388):

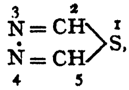


Benzenyl amidoxime. Benzenylazosulphime sulphydrate, m.p. 162°.

Azosulphime anilides are formed when phenyl mustard oil is used.

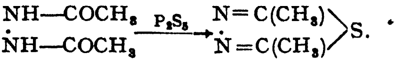
Dibenzenylazosulphime,  results from the action of iodine or persulphate upon thio-benzamide (B. **25**, 1586; J. pr. Ch. [2], **69**, 44).

Dibenzenylazoselenime,  m.p. 85°, from seleno-benzamide with iodine (B. **37**, 2551).

19. THIO-[BB$_1$]-DIAZOLE, 

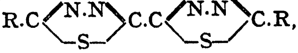
$$\begin{array}{l}\overset{3}{\dot{N}}=\overset{2}{C}H\diagdown \\ \underset{4}{\dot{N}}=\underset{5}{C}H\diagup\end{array}\!\!\overset{1}{S},$$

Derivatives of thiodiazole are obtained similarly to the furo- and pyrrodiazoles from *sym*-diacidylhydrazines by heating with P_2S_5 (B. **32,** 797; J. pr. Ch. [2], **58,** 130):



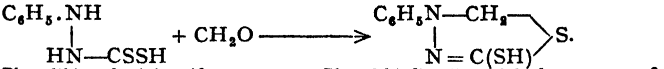
$$\begin{array}{l}\dot{N}H\text{—}COCH_3 \\ \dot{N}H\text{—}COCH_3\end{array}\xrightarrow{P_2S_5}\begin{array}{l}N=C(CH_3)\diagdown \\ \dot{N}=C(CH_3)\diagup\end{array}\!S.$$

Dimethylthio-[bb$_1$]-diazole, m.p. 64°, b.p. 203°; **diphenylthio-[bb$_1$]-diazole,** m.p. 142°, b.p.$_{17}$ 259°, from diaceto- and dibenzo-hydrazide; for homologues, see J. pr. Ch. [2], **69,** 158, 381, 481, etc.

Dimethyl- and **Diphenyl-bisthio-[bb$_1$]-diazole,**  $R.C\langle\begin{smallmatrix}N.N\\S\end{smallmatrix}\rangle C.C\langle\begin{smallmatrix}N.N\\S\end{smallmatrix}\rangle C.R$, m.p. 238° and 252°, from diacetyl- and dibenzoyloxalhydrazide with P_2S_5 (J. pr. Ch. [2], **70,** 429).

Dimethyl- and **Diphenyl-seleno-[bb$_1$]-diazole,** m.p. 77° and 156°, from diaceto- and dibenzo-hydrazide by heating with phosphorus penta-selenide (J. pr. Ch. [2], **69,** 509).

The **thiodiazolines** are derivatives of *dihydro-thio*[bb$_1$]*diazole*. They result (1) from the action of aldehydes upon phenylthiocarbazinic acid (Vol. II.), or, better, their ethers (B. **28,** 2635):



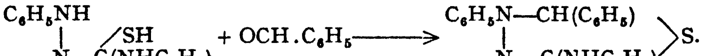
$$\begin{array}{l}C_6H_5.NH \\ \quad| \\ HN\text{—}CSSH\end{array} + CH_2O \longrightarrow \begin{array}{l}C_6H_5N\text{—}CH_2\diagdown \\ \quad\;| \\ \quad N=C(SH)\diagup\end{array}\!S.$$

Phenylthiocarbazinic acid. 3-Phenylthiodiazoline sulphydrate, m.p. 112°.

(2) By reduction of dithiodiazoline sulphohydrates (J. pr. Ch. [2], **60,** 28; **67,** 246).

The thiodiazoline sulphydrates formed in this manner are very acid. They are stable towards acids. Aqueous alkalies decompose them. They oxidize quite easily to *disulphides*. See (B. **29,** 2127) for the rearrangement of the latter.

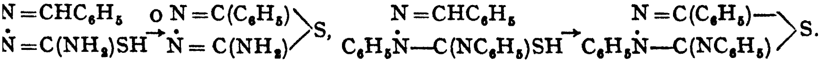
Amino-derivatives of the thiodiazolines are prepared from the thiosemicarbazides with aldehydes (B. **30,** 849):



$$\begin{array}{l}C_6H_5NH \\ \;\;|\quad\diagup SH \\ N=C(NHC_6H_5)\end{array} + OCH.C_6H_5 \longrightarrow \begin{array}{l}C_6H_5N\text{—}CH(C_6H_5)\diagdown \\ \quad\;| \\ \quad N=C(NHC_6H_5)\diagup\end{array}\!S.$$

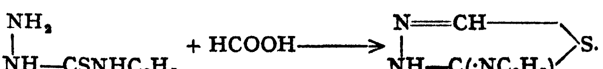
Diphenylthiosemicarbazide. Anilinophenylthiodiazoline, m.p. 160°.

Analogously, the oxidation of benzal thio-semicarbazone produces aminophenylthio-[*ab*]-diazole, and *unsym.*-benzal-*a*δ-diphenylsemicarbazone gives diphenylthiodiazoline-anil (B. **34,** 324):



$$\begin{array}{l}N=CHC_6H_5 \\ \dot{N}=C(NH_2)SH\end{array}\xrightarrow{O}\begin{array}{l}N=C(C_6H_5)\diagdown \\ \dot{N}=C(NH_2)\diagup\end{array}\!S,\quad \begin{array}{l}N=CHC_6H_5 \\ C_6H_5\dot{N}\text{—}C(NC_6H_5)SH\end{array}\rightarrow\begin{array}{l}N=C(C_6H_5)\text{—}\diagdown \\ C_6H_5\dot{N}\text{—}C(NC_6H_5)\diagup\end{array}\!S.$$

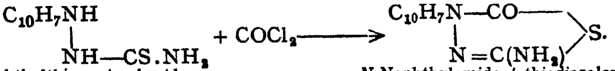
(1) *Iminothiodiazolines,* (2) *ketothiodiazolines* or *pseudo-thiodiazolones,* and (3) *dithiodiazolines* are made by the action of carboxylic acids, $COCl_2$ and CS_2, upon thiourea- and dithio-carbamic acid derivatives of the hydrazines (**24,** 4190; **27,** 613, 2512; **29,** 2483):

(1) 

$$\begin{array}{l}NH_2 \\ | \\ NH\text{—}CSNHC_6H_5\end{array} + HCOOH \longrightarrow \begin{array}{l}N\!=\!=CH\text{———}\diagdown \\ | \\ NH\text{—}C(:NC_6H_5)\diagup\end{array}\!S.$$

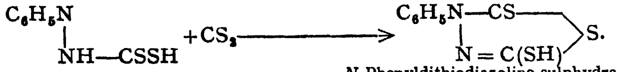
Phenylthiosemicarbazide. Phenyliminothiodiazoline, m.p. 173°.

Iminothiodiazoline, $\overline{\mathrm{S.C(NH).NH.N : C}}\mathrm{H}$, melting at 191°, is obtained from formylthiosemicarbazide (B. **29,** 2511). It is remarkable hat the acidylthiosemicarbazides, when deprived of water by acetyl chloride, yield thiodiazolines, but when heated above their melting-point, mercaptotriazoles result:

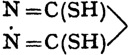
(2) 

Naphthylthiosemicarbazide.

N-Naphthylamido-ψ-thiodiazolone, m.p. 250°.

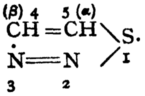
(3) 

N-Phenyldithiodiazoline sulphydrate, m.p. 91°.

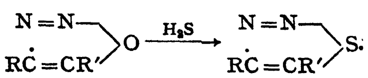
The simplest dithiodiazoline sulphydrate, obtained from hydrazine and carbon bisulphide with alc. potash, is probably **thio-[bb$_1$]-diazole dithiol,**  $\begin{matrix}\mathrm{N=C(SH)}\\ \mathrm{N=C(SH)}\end{matrix}\!\!>\!\mathrm{S}$, m.p. 168° with dec. Oxidized with KMnO$_4$, t yields thiodiazole-disulphonic acid, $N_2C_2(SO_3H)_2S$.

By oxidation with iodine the thiodiazole-sulphydrates yield disulphides of the type " Diaz.—S—S—diaz." These are split up by ammonia and amines in a peculiar manner, forming the so-called hydrosulphamines, diaz.SNH$_2$, derived from a thio-hydroxylamine, HS.NH$_2$. The aromatic hydro-sulphamines, diaz.SNHC$_6$H$_5$, transpose into *p*-amino-phenyl-thiols, NH$_2$.C$_6$H$_4$.biaz. Concerning this and other transformations of thiodiazolines, see J. pr. Ch. [2], **60,** 25; **61,** 330.

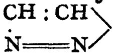
20. THIO-[AB]-DIAZOLES,



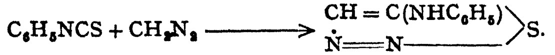
These compounds are formed from the furo-[*ab*]-diazoles or diazo-anhydrides by the action of SH$_2$ in the presence of alkali, which first splits the furo-diazole ring:



They are feebly basic and stable towards acids. Alkalies or reducing agents decompose them with formation of SH$_2$. With HgCl$_2$ they give crystalline compounds. They also combine with methyl iodide.

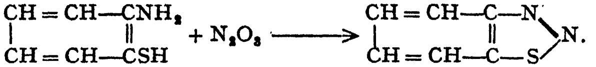
Thio-[ab]-diazole,  $\begin{matrix}\mathrm{CH : CH}\\ \mathrm{N{=\!=}N}\end{matrix}\!\!>\!\mathrm{S}$, b.p. 137°, D$_0$ 1,32, **α-Methyl-** and **α-Phenylthio-[ab]-diazole,** b.p. 184°, m.p. 53°, result from their carboxylic acids. **α-Methyl-** and **α-phenyl-thiodiazolecarboxylic ester,** m.p. 35° and 42°, from diazo-aceto-acetic ester and diazo-benzoyl acetic ester anhydride with SH$_2$. The α-methyl-thio-[*ab*]-diazolecarboxylic acid is oxidized by permanganate to **thio-[ab]-diazoledicarboxylic acid,** which on melting gives in the first instance **thio-[ab]-diazol-β-carboxylic acid.** **α-Methyl-β-acetylthio-[ab]-diazole,** an oil, is formed from diazoacetyl acetone anhydride. **α-Phenyl-β-acetyl-** and **α-methyl-β-benzoylthio-[ab]-diazole,** m.p. 70° and 43°, are formed together from diazobenzoyl acetone anhydride (A. **325,** 169; **338,** 1).

Another derivative of the thio-[*ab*]-diazoles is the addition product of phenyl mustard oil with diazomethane (B. **29,** 2588):



Anilino-thio-[*ab*]-diazole, m.p. 172° with dec.

The **phenylene diazosulphides** are *benzo*-derivatives of thio[*ab*]-diazole. They correspond to the diazo-oxides and azoimides. They are produced when nitrous acid acts upon *o*-aminothiophenols:

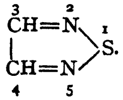


o-Amino-thiophenol. Phenylene diazosulphide.

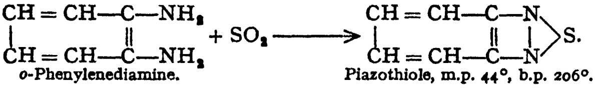
The diazosulphides are more stable than the diazo-oxides. They resemble the azoimides more particularly, as they only give up their nitrogen at higher temperatures, and then without deflagration. In doing this they yield diphenylene disulphides, $C_6H_4<^{S}_{S}>C_6H_4$. The diazosulphides are feeble bases, and take up alkyl iodides (A. **277,** 214).

Phenylene diazosulphide, $C_6H_4N_2S$, melts at 35° and boils at 129° (10 mm.). **Cumylene diazosulphide,** $C_6H(CH_3)_3N_3S$, melts at 85°.

21. THIO-[AA]-DIAZOLE,



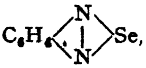
The benzo-derivatives of this thiodiazole (*piazothioles*) are formed upon treating the *o*-phenylenediamines with sulphurous acid (B. **22,** 2895):



o-Phenylenediamine. Piazothiole, m.p. 44°, b.p. 206°.

The piazothioles are feebly basic bodies, which are very stable towards oxidants. The *o*-diamines result from their reduction.

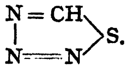
The *piaselenoles* correspond to the piazothiols. They are similarly formed from *o*-diamines and selenious acid. In their stability they resemble the piazothioles.



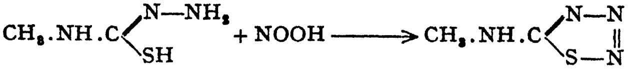
Piaselenole, $C_6H_4<^{N}_{N}>Se$, melts at 76°.

Tolupiaselenole, $C_7H_6(N_2Se)$, melts at 73° and boils at 267°.

22. THIO-[ABB₁]-TRIAZOLES



A series of compounds may be referred to this ring (*thiotriazoles* or *triazosulpholes*). They result from the action of nitrous acid upon thiosemicarbazide and alkyl thiosemicarbazides, whereas phenylthiosemicarbazide yields a tetrazole compound (B. **29,** 2491):

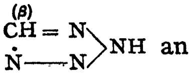


The aminotriazosulpholes formed in this manner decompose, when boiled with water, into sulphur, nitrogen, and cyanamides, while with concentrated hydrochloric acid they yield nitrogen and *thiocyanamides:*

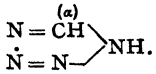
Methylamino-, ethylamino-, and **allylamino-triazosulpholes** melt at 96°, 67°, and 54°. **Amino-triazosulphole,** from thiosemicarbazide and N_2O_3, deflagrates at 129°.

23. TETRAZOLES.

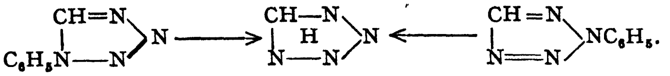
Pyrro-[aa₁b]- and **-[abb₁]-triazols,**



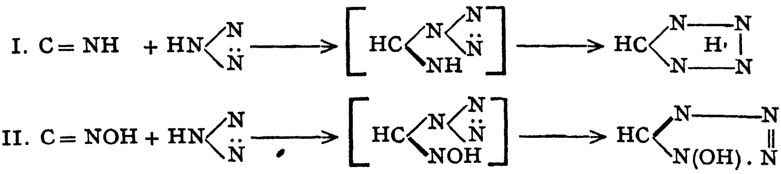
and



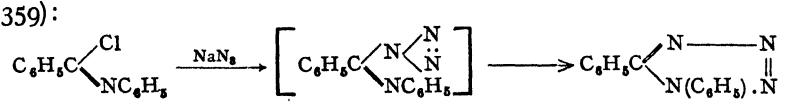
—These two possible isomeric groups of pyrro-triazoles are comprised under the name Tetrazoles; as in the case of the triazoles, the syntheses of the tetrazoles do not always offer a sure indication of their constitution (B. **29,** 1846). An *N*-phenyl-pyrro-[*aa*₁*b*]-triazole and an *N*-phenyl-pyrro-[*abb*₁]-triazole are known with certainty, but, on eliminating the phenyl groups by oxidation, these yield the same tetrazole:



Tetrazoles are formed: (1) By the condensation of azoimide with prussic acid and its derivatives, like fulminic acid, *iso*nitriles, cyanogen bromide, and cyano-formic ester, probably with intermediate formation of imidazides and hydroximic acid azides (B. **43,** 2219; C. 1910, I. 1794; 1911, I. 662, 1297):

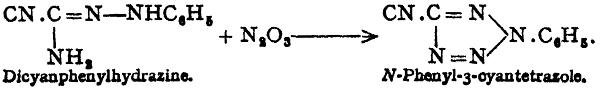


(2) The primary formation of imidazides is also the base of the formation of tetrazoles by the transposition of imido-chlorides and similar compounds with sodium azide (C. 1909, I. 1316; B. **42,** 3359):



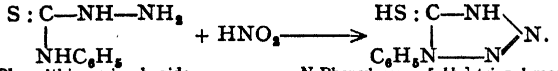
In amino-carbimide-azide, $NH_2C(:NH)N_3$ (from amino-guanidine and nitrous acid), the easy transition into amino-tetrazole has been observed directly (A. **314,** 339).

(3) By the action of nitrous acid upon hydrazidines (amidrazones)—*e.g.*, benzenylhydrazine (B. **27,** 995), dicyanophenylhydrazine (Bladin, B. **19,** 2598), amino-guanidine (A. **273,** 144). This is similar to the formation of triazoles from the same compounds with carboxylic acids:



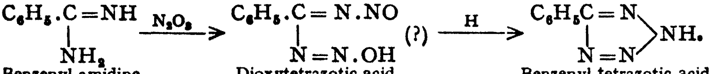
Dicyanphenylhydrazine. *N*-Phenyl-3-cyantetrazole.

A tetrazole derivative which might be derived from pyrro[abb_1]-triazole is produced in the action of HNO_2 upon phenylthiosemicarbazide (B. **28,** 74):



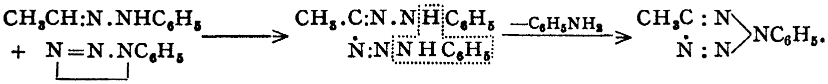
Phenylthiosemicarbazide. *N*-Phenyl-pyrro-[abb_1]-triazol-mercaptan.

(4) With nitrous acid the amidines yield dioxytetrazotic acids. These, on reduction, become oxytetrazotic and tetrazotic acids. The latter are identical with the tetrazoles which are formed by the first method (A. **263,** 101; B. **27,** 994):



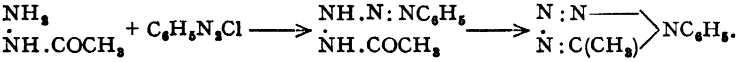
Benzenyl amidine. Dioxytetrazotic acid. Benzenyl tetrazotic acid, Phenyltetrazole.

(5) By the condensation of phenylazoimide with aldehyde phenylhydrazones by means of Na alcoholate in alcoholic solution, aniline being evolved (B. **43,** 2899):



This synthesis is a parallel to the formation of osotriazoles from osazones.

(6) From the diazo-hydrazides obtained by the reaction of mono- and diacyl-hydrazines with diazonium salts, under the action of alkalies:

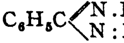


(7) Finally, the tetrazoles are prepared by oxidizing suitable tetrazolium compounds, the oxidation products of formazyl derivatives (see below).

Behaviour.—The tetrazole ring, composed of four N-atoms and one C-atom, shows in general equal stability with azoles, containing less nitrogen. Thus, the *N*-phenylated derivatives, just as with the pyrazoles and the triazoles, can be converted by nitration into nitrophenyltetrazoles, and the amino-bodies from these may be oxidized to tetrazoles. The feebly basic character of pyrrole becomes in tetrazole a strong acid, due to the influence of the N-atoms. After comparing pyrrole in many respects with phenol, tetrazole may be arranged side by side with trinitrophenol. The *silver* and *copper* salts deflagrate violently on heating.

Tetrazole, CN_4H_2 (for constitution, see above), m.p. 156°, capable of sublimation, is obtained (1) from hydronitric acid and prussic acid; (2) by treating diazo-tetrazole with alcohol (A. **287,** 243); (3) by oxidizing tetrazole mercaptan with nitric acid; (4) by oxidizing *N*-amino-phenyl-pyrro-[aa_1b]-triazole (B. **25,** 1412), or *N*-amino-phenyl-pyrro-[abb_1]-triazole (B. **34,** 3120); (5) by oxidizing di-*p*-oxyphenyl tetrazolium betaïne; finally (6) by oxidizing the so-called naphtho-tetrazole, a combined quinoline-tetrazolering (B. **33,** 1890). *Sodiumsalt,* $CN_4HNa + H_2O$, *barium salt,* $(CN_4H)_2Ba + 3\frac{1}{2}H_2O$. Heating with conc. HCl decomposes tetrazole into CO_2, N_2, and $2NH_3$.

C-Phenyl-tetrazole, *benzenyl-tetrazolic acid,* $C(C_6H_5)N_4H$, decomposes on careful heating to 218°, forming diphenyltriazole and diphenyltetrazine (A. **298,** 96). It is obtained from benzenyl-dioxytetrazolic acid or from benzenyl-hydrazidine. Similar processes yield **C-tolyl-, C-furyl-,** and **C-anisyl-tetrazole** from the corresponding hydrazidines or amidines (B. **28,** 465; A. **298,** 105). **N-Methyl-** and **N-ethyl-pyrro-[abb₁]-triazole,** m.p. 37° and b.p.$_{14}$ 156°, from the *iso*nitriles and hydronitric acid. **N-Phenylpyrro-[aa₁b]-triazole,** $C_6H_5.N.N:CH.N:N$, Oil, from its carboxylic acid. **N-Phenylpyrro-[abb₁]-triazole,** $C_6H_5.N.CH:N.N:N$, m.p. 66°, from phenyl *iso*cyanide and N_3H, from diformylhydrazine and diazo-benzene chloride in alkaline solution, and from its mercaptan, by oxidizing it with chromic acid (B. **34,** 3120). **N-Phenyl-α-methylpyrro-[abb₁]-triazole,** $C_6H_5N.C(CH_3):N.N:N$, m.p. 97·5°, from acetyl- and diacetylhydrazine by method 6. **N-Phenyl-β-methylpyrro-[aa₁b]-triazole,** $C_6H_5.N.N:C(CH_3).N:N$, m.p. 40°, by method 5. **N,α-Diphenylpyrro-[abb₁]-triazole,** $C_6H_5N.C(C_6H_5):N.N:N$, m.p. 146°, is formed by transposing benzanilide-imide chloride with sodium azide; from benzo-hydrazide and diazobenzene chloride by method 6, and from the transposition product of benzophenone chloride with sodium azide by an atomic displacement recalling Beckmann's transformation (B. **43,** 3359). **N,β-Diphenyl-pyrro-[aa₁b]-triazole,** $C_6H_5N.N:C(C_6H_5).N:N$, m.p. 107°, is obtained from benzaldehyde phenylhydrazone and $C_6H_5N_3$; by oxidation of *p*-hydroxyphenyl-diphenyl-tetrazolium hydroxide with $KMnO_4$; and from the so-called guanazyl-benzene,

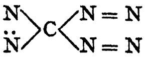


$C_6H_5C\begin{smallmatrix}\diagup N.NH(CN_2H_3) \\ \diagdown N:NC_6H_5\end{smallmatrix}$, by oxidation with N_2O_3 or nitric acid (B. **30,** 449). It is distinguished by great stability (B. **29,** 1854).

Bis-tetrazole, $(CHN_4)_2$ (?), results from the addition product of cyanogen and hydrazine with N_2O_3 (B. **26,** R. 891).

C-Bromo-tetrazole, BrC_2HN_4, m.p. 148°, from cyanogen bromide and azoimide.

C-Amino-tetrazole, *amino-tetrazotic acid,* $C(NH_2)N_4H$, m.p. 203°, results from diazo-guanidine nitrate with nitrous acid, with intermediate formation of amido-carbimide azide, and yields **diazo-tetrazole** on further action of nitrous acid. Diazo-tetrazole explodes in conc. aqueous solution even at 0°, and probably has the following constitution:



$\begin{smallmatrix}N \\ \vdots \\ N\end{smallmatrix}\!>\!C\!<\!\begin{smallmatrix}N=N \\ N=N\end{smallmatrix}$ (compare diazo-indazoles, etc.); with metallic oxides, stable salts are formed of the type $C(N:N.OMe)N_4Me$. A reduction of the diazo-tetrazole produces **tetrazyl-hydrazine,** $C(NHNH_2)N_4H$, m.p. 199° with dec. The latter is decomposed by nitrous acid into **tetrazyl**

azoimide, $C(N_3)N_4H$, a beautifully crystalline but exceedingly explosive substance (A. **287,** 238). Oxidation of amino-tetrazole in strongly alkaline solutions with $KMnO_4$ produces salts of **azo-tetrazole,** (HN_4C)-$N : N(CN_4H)$, which is very unstable in the free condition, and is converted by mineral acids into tetrazyl-hydrazine, nitrogen, and formic acid, and by reduction with Mg powder into **hydrazo-tetrazole,** $(HN_4C)NH(CN_4H)$, a white powder exploding on heating.

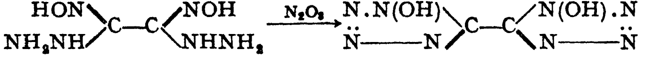
On treating solutions of hydrazo-tetrazole or azo-tetrazole with bromine, nitrogen is evolved, and the first result is **dibromo-formal-tetrazyl-hydrazone** (1), m.p. 177°, and then *iso*-**cyano-tetra-bromide** (2), m.p. 42° (see Vol. I. and A. **303,** 57):

$$(HN_4C)N : N(CN_4H) \xrightarrow{(1)} (HN_4C)NH.N : CBr_2 \xrightarrow{(2)} Br_2C : N.N : CBr_2.$$

C-**Anilino-*N*-phenyltetrazole,** $C_6H_5NH.CN_4.C_6H_5$, m.p. 163°, and its homologues are obtained from the amido-diaryl guanidins with N_2O_3 (B. **38,** 1061).

N-**Hydroxypyrro-[abb₁]-triazole,** from fulminic acid and N_3H, decomposes with deflagration at 145°. *α*-**Phenyl-*N*-hydroxypyrro-[abb₁]-triazole,** m.p. 121° with dec., is formed from benzo-hydroximic acid chloride and sodium azide, as well as from benzo-hydrazide oxime with nitrous acid, probably with intermediate formation of the unstable benzo-hydroximic acid azide. *N*-**Phenyl-*α*-hydroxypyrro-[abb₁]-triazole,** $C_6H_5N.C(OH) : N.N : N$, m.p. 187°, from hydrazodicarboxylic ester by method 6.

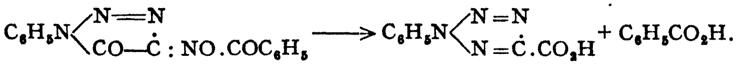
C-**Bis-*N*-hydroxytetrazole** explodes very violently at 176° and on rubbing; it is formed from oxalhydrazide oxime and nitrous acid (B. **42,** 4201):



$$\begin{matrix}HON\\NH_2NH\end{matrix}>C—C<\begin{matrix}NOH\\NHNH_2\end{matrix} \xrightarrow{N_2O_3} \begin{matrix}N.N(OH)\\\ddot{N}——N\end{matrix}>C—C<\begin{matrix}N(OH).N\\N——\ddot{N}\end{matrix}$$

Tetrazole-*C*-carboxylic ethyl ester, $(CO_2C_2H_5)CN_4H$, m.p. 86°, from cyano-formic acid ester and N_3H, yields tetrazole on saponification.

N-**Phenyl-pyrro-[aa₁b]-triazole-*β*-carboxylic acid,** $C_6H_5N.N : C(COOH).N : N$, m.p. 138°, is formed by saponifying *N*-phenyl-cyano-tetrazole; or from glyoxylic acid phenyl hydrazone by method 5; and by a peculiar atomic displacement from the *N*-phenylbenzoyloximino-pyrro-[*ab*]-diazolone on treating with cold NaHO (B. **41,** 4055):

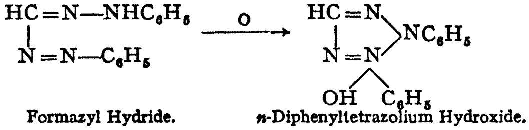


$$C_6H_5N<\begin{matrix}N{=\!=}N\\CO—\dot{C} : NO.COC_6H_5\end{matrix} \longrightarrow C_6H_5N<\begin{matrix}N=N\\N=\dot{C}.CO_2H\end{matrix} + C_6H_5CO_2H.$$

Tetrazyl mercaptan, $HS.CN_4H$, m.p. 205° with dec., results from its methyl ether, $CH_3S.CN_4H$, m.p. 151° with dec., by heating with HI. This ether is obtained from methyl-thio-semicarbazide, $CH_3SC<\begin{matrix}NH_2\\NNH_2\end{matrix}$ with N_2O_3. The mercaptan on oxidation with HNO_3 yields tetrazole, but with $KMnO_4$ **tetrazole sulphonic acid,** $C(SO_3H)N_4H$, which yields *C*-oxy-tetrazole, $C(OH)N_4H$, m.p. 254°, on fusion with potash (B. **34,** 3110).

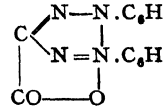
N-**Phenyl-α-thiotetrazoline,** $S:C—NH—N=N—N.C_6H_5$ (?), melting with decomposition at 142°–145°, is formed from phenylthiosemicarbazide when acted upon with nitrous acid. Digestion with caustic soda converts it into isomeric **phenyltetrazyl mercaptan,** $HS.C=N—N=N—N.C_6H_5$, melting at 150°. Both compounds yield the same silver salt, which methyl iodide converts into N-*phenyltetrazyl methyl sulphide.* Potassium permanganate produces *N*-phenyltetrazole sulphonic acid, $C(SO_3H)N\ C_6H_5$, which, upon heating with hydrochloric acid, splits off the sulpho-group and becomes 1-*phenyl*-5-*hydroxytetrazole,* $OH.C=N—N=N—NC_6H_5$, melting at 186°.

Tetrazolium compounds are those which result from the oxidation of formazyl bodies in a manner similar to that by which the azoammonium derivatives are obtained from the *o*-anilino-bodies (B. **27,** 2920), and the osotetrazones from the osazones:

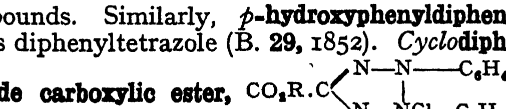


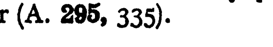
Formazyl Hydride. *n*-Diphenyltetrazolium Hydroxide.

The oxidation is best effected by amyl nitrite and hydrochloric acid. The tetrazolium hydroxides are, like all ammonium hydroxides, strong bases. Ammonium sulphide reduces them to formazyl compounds.

N-**Diphenyltetrazolium chloride,** $CHN_4(C_6H_5)_2Cl$, melting with decomposition at 268°, results by the elimination of carbon dioxide from **diphenyl-tetrazolium chloride carboxylic acid,** melting at 257° with decomposition. The ester of this acid is prepared from formazyl carboxylic ester, and passes just as readily as the acid into a betaïne, 

p-**Dihydroxydiphenyl-tetrazolium betaïne,** formed in an analogous manner, melts at 179° with decomposition, and can be oxidized to tetrazole (B. **28,** 1693):

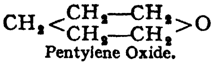


which demonstrates the connection between the tetrazoles and tetrazolium compounds. Similarly, *p*-**hydroxyphenyldiphenyltetrazolium chloride** yields diphenyltetrazole (B. **29,** 1852). *Cyclo***diphenylenetetrazolium chloride carboxylic ester,**  is derived from *cyclo*formazyl carboxylic ester (A. **295,** 335).

4. SIX-MEMBERED HETEROCYCLIC COMPOUNDS.

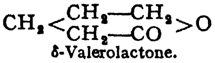
A. MONOHETERO-ATOMIC SIX-MEMBERED RINGS.

1. *Six-Membered Rings with an O-Member.*—A series of cyclic bodies belongs here. They have already been discussed, according to their character, either with the fatty bodies or fatty aromatic substances with open chain, with which they are genetically related. They are the *anhydrides of ϵ-glycols* (I. 318), the *δ-lactones—e.g., δ-valerolactone* (I. 374)—the *anhydrides of the glutaric acids* (I. 502), etc.:



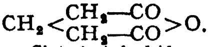
$CH_2<\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}>O$

Pentylene Oxide.



$CH_2<\begin{matrix}CH_2—CH_2\\CH_2—CO\end{matrix}>O$

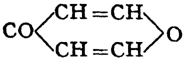
δ-Valerolactone.



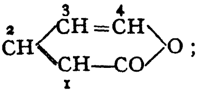
$CH_2<\begin{matrix}CH_2—CO\\CH_2—CO\end{matrix}>O.$

n-Glutaric Anhydride.

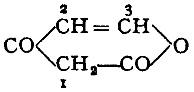
These are unsaturated δ-lactones and acid anhydrides corresponding to the saturated δ-lactones and δ-acid anhydrides. Anhydrides of unsaturated ϵ-glycols are not known, but there are anhydrides of diolefine dihydroxyketones. They are the γ-**pyrones,** which are isomeric with the diolefine-δ-oxy-acid lactones, the α-**pyrones:**



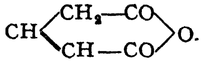
γ-Pyrone.



α-Pyrone.

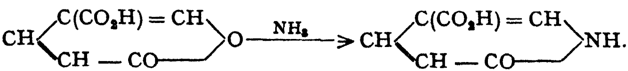


α,γ-Pyronone.

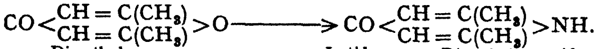


Glutaconic Anhydride.

The pyrones and allied compounds are characterized by the fact that when they are digested with ammonia the linking oxygen atom is replaced by NH, and *pyridones* or *hydroxypyridines* (p. 171) result:



α-Pyrone Carboxylic Acid, Coumalic Acid. Hydroxypicolinic Acid.



$$CO<\begin{matrix}CH=C(CH_3)\\CH=C(CH_3)\end{matrix}>O \longrightarrow CO<\begin{matrix}CH=C(CH_3)\\CH=C(CH_3)\end{matrix}>NH.$$

Dimethyl-γ-pyrone. Lutidone, α,α₁-Dimethyl-γ-pyridone.

(*a*) The *coumalins* belong to the α-pyrones:

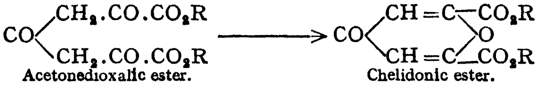
α-**Pyrone, Coumalin,** $C_5H_4O_2$, and 2,4-**Dimethyl-α-pyrone, dimethyl coumalin,** $C_5H_2(CH_3)_2O_2$ (I. 362), are obtained from their acids:

Coumalic Acid, $C_5H_3O_2.CO_2H$, made by the action of concentrated sulphuric acid upon malic acid, and **Dimethylcoumalic acid,** iso-*dehydracetic acid, 2,4-dimethyl-α-pyrone-3-carboxylic acid,* $C_5H(CH_3)_2O_2$-COOH, obtained from aceto-acetic ester with H_2SO_4, and by transforming sodium aceto-acetic ester with β-chlorocrotonic acid ester (see Vol. I.). On **ethoxycoumalindicarboxylic acid ester,** $C_5HO_2(OC_2H_5)(COOC_2H_5)_2$, m.p. 94°, from dicarboxy-glutaconic acid ester, and others, see A. **297,** 86; J. pr. Ch. [2], **58,** 404. **Phenylcoumalin, 1-phenyl-α-pyrone,** $C_5H_3(C_6H_5)O_2$, m.p. 68°, is found in *Coto* bark. On reduction it yields δ-phenyl valerianic acid, and with ammonium acetate α-phenyl pyridone (B. **29,** 1673, 2659). **α-Pyrone-4-carboxylic acid,** m.p. 228°, results from treating oxal-crotonic acid ester with alkalies (C. 1900, II. 174). **1-Phenyl-α-pyrone-4-carboxylic acid ester,**

from phenylpropargylidenemalonic acid ester (B. **36,** 3671). A series of α-pyrone derivatives has been obtained by the condensation of acetylene carboxylic esters with β-diketones or β-ketonic acid esters and sodium ethylate (C. 1899, II. 608, etc.). **4-Methyl-α-pyrone-1,3-dicarboxylic acid ester,** $C_5HO_2(CO_2C_2H_5)_2(CH_3)$, m.p. 80°, by condensation of ethoxy-methylene malonic ester with sodium aceto-acetic ester (C. 1908, II. 523).

From the α,γ-pyronones (see above) are derived: **Dehydracetic acid,** 1-*aceto*-3-*methyl pyronone*, $CH_3C:CH.CO.CH(COCH_3)CO.O$ (B. **48,** 1070), obtained by boiling aceto-acetic ester, and by polymerizing ketene, $CH_2=CO$ (B. **41,** 597), and therefore also from acetyl chloride with tertiary bases (A. **323,** 247) and by the action of P_2O_5 upon boiling acetic anhydride (B. **40,** 362). It is also formed by detaching CO_2 from **dehydraceto-carboxylic acid,** 1-*aceto*-3-*methylpyronone-2-carboxylic acid*, obtained from acetone dicarboxylic acid with acetic anhydride (A. **373,** 186). On heating with conc. H_2SO_4, dehydracetic acid passes into **triacetic acid,** 3-*methylpyronone* (B. **24,** R. 857), which, in turn, is converted into dehydracetic acid by heating with acetic anhydride and sodium acetate (B. **37,** 3387). Further, α,γ-pyronones have been obtained by the action of tertiary bases upon mono-alkyl-acetyl chlorides (A. **378,** 261).

(*b*) γ-Pyrones result in general from α,γ,ε-triketones by elimination of H_2O (B. **24,** 111):



Acetonedioxalic ester. Chelidonic ester.

Conversely, they are easily reconverted into triketones by alkalies. Though the pyrones contain a ketone-oxygen atom, they do not react with hydroxylamine, etc. (compare xanthones), neither do halogens add themselves to the pyrones. The pyrones, especially dimethyl pyrone, possess the peculiar property of combining with acids and metal haloids to salt-like addition products which easily dissociate again into their components. This fact has been used to support the quadri-valence of the oxygen in these compounds (compare Cineol, C. 1900, II. 313; A. **364,** 1; **376,** 217).

γ-Pyrone, *pyrocomane*, $C_5H_4O_2$, m.p. 32°, b.p. 315°, results from its carboxylic acids, comanic and chelidonic acid, by the loss of CO_2 on heating (B. **37,** 3744). Pyrone, which may be regarded as an anhydride of bishydroxymethyleneacetone, CH(OH):CH.CO.CH:CH(OH), can easily be split up into its derivatives; thus we obtain, with NaHO and benzoyl-chloride, dibenzoyl bishydroxymethyleneacetone; with K methylate the K-salt of bishydroxymethyleneacetone monomethyl ether; and, by acetalizing with orthoformic acid ester and HCl, the hexa-ethylacetal of diformyl acetone (compare the splitting up of furan into succino-dialdehyde tetra-methyl acetal). Pyrone is easily regenerated from the derivatives of bishydroxymethylene acetone (B. **38,** 1461). **Mono-** and **dibromo-pyrone,** m.p. 114° and 157° respectively, are obtained by the action of undiluted bromine upon pyrone (B. **38,** 3562). **αα₁-Dimethyl-γ-pyrone,** $C_5H_2(CH_3)_2O_2$, m.p. 132°

(subliming even at 80°), b.p. 248°, is formed from dehydracetic acid on heating with HI, or from its dicarboxylic acid (see below) (A. **257,** 253). *Hydrochloride,* $C_7H_8O_2.HCl + 2H_2O$; *chloroplatinate,* $(C_7H_8O_2)_2H_2PtCl_6$; *oxalate* $(C_7H_8O_2)C_2O_4H_2$. On boiling with barium hydrate it yields diacetyl-acetone; and with methyl iodide, dimethyldiacetyl acetone, which, on heating with HCl, passes into **tetramethyl-γ-pyrone,** $C_5(CH_3)_4O$, m.p. 92° (C. 1900, II. 313). On heating with ammonia, dimethyl pyrone forms lutidone (see below).

α-Phenyl-α₁-methyl-γ-pyrone, m.p. 88°, and **αα₁-diphenyl-γ-pyrone,** m.p. 139°, have been obtained by the condensation of phenyl-propiolic acid ester with acetone and acetophenone respectively (C. 1908, I. 1703).

β-Hydroxy-γ-pyrone, *pyrocomenic* or *pyromeconic acid,* $C_5H_3(OH)O_2$, m.p. 121°, b.p. 228°, is formed by the distillation of its carboxylic acids, comenic and meconic acid. With bases it forms unstable salts. With N_2O_3 there results an *iso*-nitroso-compound derivable from the tautomeric keto-form, $CO<\begin{smallmatrix}CO.CH_2\\CH:CH\end{smallmatrix}>O$, and passing, on reduction into pyro-mecazonic acid, *αβγ*-trihydroxypyridine (C. 1902, I. 1365). **α-Methyl-β-hydroxy-γ-pyrone, maltol,** m.p. 159°, has been found in the needles of pines and the bark of larches, and is also formed on roasting malt (B. **36,** 3407; C. 1905, II. 680).

Pyrone-α-carboxylic Acid, **Comanic Acid,** $C_5H_3O_2.CO_2H$, is obtained from chelidonic acid by the loss of carbon dioxide. It dissolves with difficulty in water. It melts at 250° and decomposes. When boiled with lime it decomposes into acetone, oxalic acid, and formic acid. It forms an hydroxypicolinic acid when digested with ammonia.

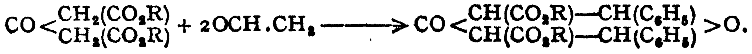
Pyrone-αα₁-dicarboxylic Acid, Chelidonic Acid, $C_5H_2O_2(CO_2H)_2$, melts at 220°, and occurs, together with malic acid, in *Chelidonium majus* (A. **57,** 274). It can be readily obtained through the loss of water from acetone-dioxalic acid. It forms colourless salts. An excess of alkali converts it into salts of acetone-dioxalic acid or **xanthochelidonic acid,** which are yellow-coloured.

The reduction of chelidonic acid gives rise to acetone-diacetic acid or **hydro-chelidonic acid,** and normal pimelic acid. Ammonia converts it into an hydroxy-pyridine dicarboxylic acid.

Hydroxy-pyronecarboxylic Acid, *Comenic Acid,* $C_5H_2(OH)(COOH)O_2$, from meconic acid, is converted by ammonia into dihydroxypicolinic or comenamic acid, which can also be obtained from **meconic acid,** $C_5H(OH)(COOH)_2O_2 + 3H_2O$, which occurs in opium in union with morphine (A. **83,** 352). It readily parts with carbon dioxide. Ferric salts colour its solutions dark red. The constitution of these acids has been determined by their decomposition products with barium hydrate (C. 1900, II. 384).

Dimethylpyronedicarboxylic Acid, $C_5(CH_3)_2(COOH)_2O_2$; its *diethyl ester,* melting at 80°, is formed by the exit of water from carbonyl diacetoacetic ester, $CO[CH(CO_2R)COCH_3]_2$ (B. **20,** 154; also B. **24,** R. 573).

Tetrahydropyrone derivatives result from the condensation of acetone dicarboxylic esters and aldehydes by means of hydrochloric acid (B. **29,** 994, 2051):

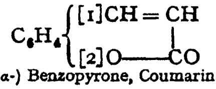


$$CO<\begin{smallmatrix}CH_2(CO_2R)\\CH_2(CO_2R)\end{smallmatrix} + 2OCH.CH_3 \longrightarrow CO<\begin{smallmatrix}CH(CO_2R)—CH(C_6H_5)\\CH(CO_2R)—CH(C_6H_5)\end{smallmatrix}>O.$$

Dimethyl- and **diphenyl-tetrahydropyrone dicarboxylic diethyl esters** melt at 102° and 115°. The free acids split off CO_2 and yield tetrahydropyrones, which are easily split up to diolefine-ketones by mineral acids; $\alpha\alpha_1$**-Diphenyl tetrahydropyrone,** m.p. 131°, gives dibenzal-acetone. In contrast to the pyrones, the tetrahydropyrones yield oximes (B. **30,** 2801; **31,** 1508; **32,** 809, 1744).

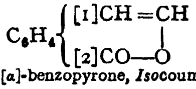
Similarly, **diphenyldimethyl tetrahydropyrone,** $C_5H_4O_2(CH_3)_2(C_6H_5)_2$, melting at 106° and boiling at 236° (20 mm.), is formed from diethyl ketone and two molecules of benzaldehyde in the presence of alcoholic potash (B. **29,** 1352).

The **coumarins** and *iso***coumarins** are *benzo-derivatives of α-pyrone:*



$$C_6H_4\begin{cases}[1]CH=CH \\ \quad | \qquad\quad | \\ [2]O\text{——}CO\end{cases}$$

(α-) Benzopyrone, Coumarin.



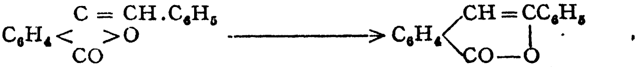
$$C_6H_4\begin{cases}[1]CH=CH \\ \quad | \qquad\quad | \\ [2]CO\text{—}O\end{cases}$$

Iso-[α]-benzopyrone, *Iso*coumarin.

The latter are more easily converted by ammonia into benzopyridone or hydroxy*iso*quinoline derivatives than the pyrones into pyridones.

Coumarin and its homologues have been discussed as lactones of *o*-hydroxycinnamic acids immediately after the latter. Iso*coumarins,* the lactones of benzene carboxylic acids, with hydroxylated side-chain unsaturated in the β-position, isomeric with the *o*-hydroxycinnamic acids, are produced by the following general methods:

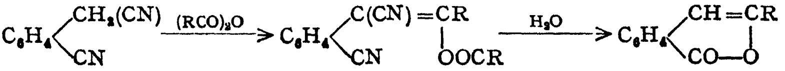
1. Benzylidene and alkylidene phthalides can be rearranged into *iso*benzalphthalides or *iso*coumarins (B. **20,** 2363; **24,** 3973):



$$C_6H_4<\begin{matrix}C=CH.C_6H_5 \\ \quad >O \\ CO\end{matrix} \xrightarrow{\qquad\qquad} C_6H_4\begin{matrix}\diagup CH=CC_6H_5 \\ \qquad\quad | \\ \diagdown CO\text{—}O\end{matrix}$$

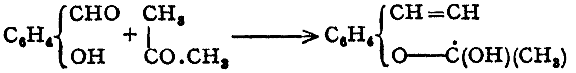
Benzalphthalide. *Iso*benzalphthalide, Phenyl*iso*coumarin.

2. When acid anhydrides or chlorides act upon *o*-cyanobenzyl cyanide, condensation products result which, upon treatment with acids, have one cyanogen group split off and the other saponified, with the production of *iso*coumarins (B. **25,** 3566; **27,** 827):



$$C_6H_4\begin{matrix}\diagup CH_2(CN) \\ \diagdown CN\end{matrix} \xrightarrow{(RCO)_2O} C_6H_4\begin{matrix}\diagup C(CN)=CR \\ \qquad\qquad | \\ \diagdown CN \qquad OOCR\end{matrix} \xrightarrow{H_2O} C_6H_4\begin{matrix}\diagup CH=CR \\ \qquad\quad | \\ \diagdown CO\text{—}O\end{matrix}$$

Benzopyranols.—Derivatives of benzo-α-pyrone, which, instead of the >CO-group of benzopyrone, contain the group $>C<\begin{matrix}OH \\ R\end{matrix}$, and are therefore called "*benzopyranols,*" are formed by the condensation of *o*-hydroxybenzaldehydes and ketones by means of acids:



$$C_6H_4\begin{cases}CHO \\ OH\end{cases} + \begin{matrix}CH_3 \\ | \\ CO.CH_3\end{matrix} \xrightarrow{\qquad} C_6H_4\begin{cases}CH=CH \\ \qquad\quad | \\ O\text{——}C(OH)(CH_3)\end{cases}$$

The simplest benzopyranols are compounds of but slight stability. Like xanthydrol and phenyl-xanthenol, they give with mineral acids and metal haloids intensely coloured compounds, many of great stability (A. **364,** 17; **370,** 196).

α-Phenyl-benzo-pyranol, from acetophenone and salicylaldehyde, is split up into its components by NaHO. αβ-Diphenyl-benzo-pyranol, m.p. 122°, from salicylaldehyde and desoxybenzoin.

Among the benzo-pyranols there is also a group of dye-stuffs formed by the condensation of multivalent phenols like resorcin, pyrogallol, phloroglucin, and hydroxyquinol with β-diketones:

$$\begin{array}{l} :CH \\ -\dot{C}(OH)(C_6H_5) \end{array}$$

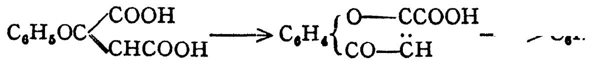
The dye-stuffs formed in the action of acetic anhydride and zinc chloride upon phenols, such as *phenaceteïn*, *resaceteïn*, and *orcaceteïn*, are also to be regarded as benzo-pyranols (B. **34**, 1189, 2368; **35**, 1799; **36**, 1941, 3607; **37**, 354, 1791; **39**, 850).

Biphenyl methalolide, $\begin{array}{l} C_6H_4.CO \\ | \quad\quad | \\ C_6H_4O \end{array}$, the lactone of *o*-hydroxydiphenyl-*o*-carboxylic acid, is to be regarded as dibenzo-α-pyrone.

From *benzo-* and *dibenzo-γ-pyrone* a large number of yellow vegetable dyes are derived (Kostanecki), some of which, like the simple γ-pyrones, form salt-like compounds with acids.

γ-Benzopyrone, $C_6H_4\left\{\begin{array}{l} [1]CO—CH\ (\alpha) \\ [2]O—\ddot{C}H\ (\beta) \end{array}\right.$.—The fundamental body of this group has been termed "chromone," while the β-phenyl benzopyrone found in many yellow vegetable dyes has been called "*flavone.*" Chromone and flavone are produced:

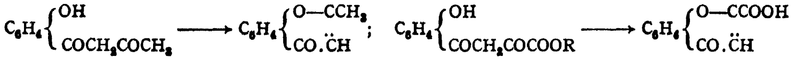
(1) From their α-carboxylic acids, obtained by condensing phenoxyfumaric acids by means of sulphuric acid (C. 1900, II. 965; 1901, I. 1009; II. 1052):



$$C_6H_5OC\begin{array}{l}\diagup COOH \\ \diagdown CHCOOH\end{array} \longrightarrow C_6H_4\left\{\begin{array}{l} O—CCOOH \\ CO—\ddot{C}H \end{array}\right. -$$

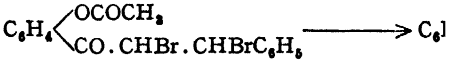
Chromone.

(2) *o*-Hydroxybenzoyl-β-ketones and *o*-hydroxybenzoylpyroracemic acid esters yield β-alkyl- or aryl-chromones and chromone-β-carboxylic acids respectively:



$$C_6H_4\left\{\begin{array}{l} OH \\ COCH_2COCH_3 \end{array}\right. \longrightarrow C_6H_4\left\{\begin{array}{l} O—CCH_3 \\ CO.\ddot{C}H \end{array}\right.; \quad C_6H_4\left\{\begin{array}{l} OH \\ COCH_2COCOOR \end{array}\right. \longrightarrow C_6H_4\left\{\begin{array}{l} O—CCOOH \\ CO.\ddot{C}H \end{array}\right.$$

(3) Flavones also result from treating benzylidene-*o*-hydroxyacetophenone dibromides with alkali:

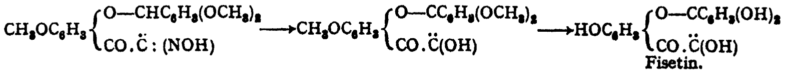


$$C_6H_4\begin{array}{l}\diagup OCOCH_3 \\ \diagdown CO.CHBr.CHBrC_6H_5\end{array} \longrightarrow C_6]$$

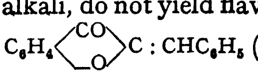
Substituted benzylidene-*o*-hydroxyacetophenones condense, either during their synthesis or on treatment with HCl, to dihydroflavones or flavanones:

$$C_2H_5OC_6H_3\left\{ OH \right. \qquad \longrightarrow \qquad \left\{ O—CHC_6H_3(OCH_3)_2 \right.$$

With N_2O_3, these flavanones yield *iso*nitroso-compounds, decomposed by hydrolysis into hydroxylamine and flavonols. In this way *fisetin*, *quercetin*, etc., have been synthesized:

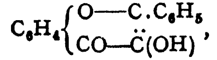
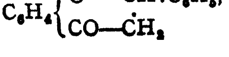


$$CH_3OC_6H_3\begin{cases}O\text{—}CHC_6H_3(OCH_3)_2\\CO.\ddot{C}:(NOH)\end{cases}\longrightarrow CH_3OC_6H_3\begin{cases}O\text{—}CC_6H_3(OCH_3)_2\\CO.\ddot{C}(OH)\end{cases}\longrightarrow \underset{\text{Fisetin.}}{HOC_6H_3\begin{cases}O\text{—}CC_6H_3(OH)_2\\CO.\ddot{C}(OH)\end{cases}}$$

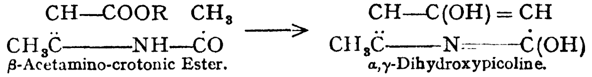
On treating with bromine and alkali many substituted benzylidene-*o*-hydroxy-acetophenones pass into flavones (B. **33**, 1478); other benzal-*o*-hydroxy-acetophenones, on treating their dibromides with alkali, do not yield flavones, but the *isomeric benzylidene coumaranones*,  $C_6H_4\langle{}^{CO}_{O}\rangle C:CHC_6H_5$ (B. **32**, 309). On the other hand, the dibromides of the benzylidene coumarones can be converted by the action of alkali under certain conditions into flavonols (B. **41**, 4233).

By heating with alkali the flavones are first split up into *o*-hydroxyphenyl-β-diketones like $C_6H_4<^{OH}_{COCH_2COC_6H_5}$, which then split up further in two directions, forming acetophenone and *o*-hydroxybenzoic acid, or *o*-hydroxy-acetophenone and benzoic acid (B. **33**, 330). The hydroxyflavones and hydroxyflavonols, many of which have been synthesized (B. **38**, 2177), mostly give a yellow coloration to china clay mordants (B. **39**, 86).

Benzo-γ-pyrone, *Chromone*, $C_6H_4[C_3H_2O_2]$, m.p. 59°, is obtained by heating its β-carboxylic acid, m.p. 251° with dec., resulting from phenoxy-fumaric acid with concentrated H_2SO_4, or from *o*-hydroxybenzoyl pyro-racemic ester with HCl (see above). **β-Methyl-chromone,** m.p. 71°, from *o*-methoxy-benzoyl acetone with HI by method 2; by the same method hydroxy-chromones have been prepared (for list see B. **35**, 2890).

Flavone, β-Phenyl-benzo-γ-pyrone, $C_6H_4[C_3O_2H(C_6H_5)]$, m.p. 97°, is obtained from benzylidene-*o*-acetoxy-acetophenone dibromide or from *o*-hydroxy-benzoyl-acetone. **Chrysin,** 1,3-*dihydroxyflavone*, $(OH_2)[1,3]$-$C_6H_2[C_3O_2H(C_6H_5)]$, m.p. 275°, occurring in the buds of various kinds of poplar, has been obtained synthetically from the condensation product of phloracetophenone-trimethyl ether, benzoic ester and $NaOC_2H_5$, by boiling with HI (B. **32**, 2448; **37**, 3167). **Apigenin,** 1,3,4′-*trioxyflavone*, $(OH)_2[1,3]C_6H_2[C_3O_2H(C_6H_4[4']OH)]$, m.p. 347°, is found in the form of the glucoside *apiïn* in parsley and celery; synthetically it is prepared from the condensation product of phloracetophenone-trimethyl ether and anisic acid ester (B. **33**, 1988, 2334; **38**, 931; A. **318**, 121). **Luteolin,** 1,3,3′,4′-*tetraoxyflavone*, $(OH)_2[1,3]$-$C_6H_2[C_3O_2H.C_6H_3[3',4'](OH)_2]$, m.p. 329°, the yellow dyestuff of mignonette, *Reseda luteola*, has been obtained by the condensation of phloracetophenone-trimethyl ether with veratric acid ester (B. **33**, 3410; **34**, 1449; **37**, 2625). The following dyestuffs are derived from *flavonol*,  $C_6H_4\begin{cases}O\text{——}C.C_6H_5\\CO\text{—}\ddot{C}(OH)\end{cases}$, light yellow needles, m.p. 170°, prepared by the hydrolytic disintegration of the *iso*-nitroso-compound of **flavanone,**  $C_6H_4\begin{cases}O\text{——}CH.C_6H_5\\CO\text{—}\dot{C}H_2\end{cases}$, m.p. 76°. The latter is obtained

by the action of sodium alcoholate upon β-acetaminocarboxylic esters (C. 1899, II. 462):



$$\begin{array}{l} \text{CH—COOR}\quad \text{CH}_3 \\ \text{CH}_3\dot{\text{C}}\text{———NH—}\dot{\text{C}}\text{O} \end{array} \longrightarrow \begin{array}{l} \text{CH—C(OH)}=\text{CH} \\ \text{CH}_3\dot{\text{C}}\text{———N}=\!=\!=\dot{\text{C}}\text{(OH)} \end{array}$$

β-Acetamino-crotonic Ester. α,γ-Dihydroxypicoline.

10. The formation of β-chloro- and β-bromopyridine from pyrrole on heating with CCl_3H or CBr_3H and $NaOC_2H_5$ is of interest. CH_2I_2 produces pyridine, and $C_6H_5CHCl_2$ β-phenylpyridine (B. **20,** 191).

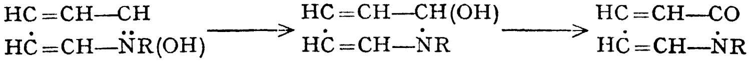
11. *N*- and α-alkylpyrroles, on conducting their vapours through tubes at low incandescence, or on heating with HCl, yield pyridines; *N*- and α-methyl pyrrole yield pyridine, and *N*-benzylpyrrole β-phenyl pyridine (B. **19,** 2196; **38,** 1946).

Behaviour.—The pyridine bases are colourless liquids with a peculiar odour. Pyridine is miscible with water. The solubility of the higher members grows rapidly less. Frequently they are more soluble in cold than in hot water.

1. *Salts.*—The platinum double salts of the formula $(C_5H_5N.HCl)_2$-$PtCl_4$ lose two molecules of hydrochloric acid upon prolonged boiling and form $(C_5H_5N)_2PtCl_4$ (see pyrazoles). The pyridines form addition compounds with many inorganic salts. These, with $HgCl_2$ and $AuCl_3$, are characteristic and serve for the separation of the individual bases (A. **247,** 1; compare C. 1897, II. 129, 311).

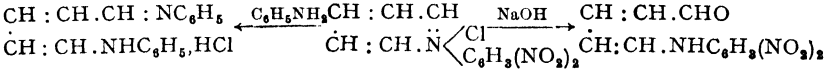
2. Alkyl iodides and pyridines form *alkylpyridinium iodides.* Like alkyl-iodide, the pyridines also add chloracetic acid and its homologues to form pyridine betaïnes (C. 1911, I. 494); also acid chlorides, cyanogen bromide, 2,4-dinitro-chloro-benzene, etc. By substituents in the $\alpha\alpha_1$-position the formation of pyridinium salts is either hindered or made impossible (C. 1905, I. 381).

On treating the alkylpyridinium iodides with NaHO, the strongly basic pyridinium hydroxides first formed transform themselves into the isomeric α-hydroxydihydro-pyridines, also rather unstable, and these are oxidized by potassium ferricyanide to *N*-alkyl-α-pyridones (J. pr. Ch. [2], **84,** 219):



$$\begin{array}{l} \text{HC}=\text{CH—CH} \\ \dot{\text{HC}}=\text{CH—}\ddot{\text{N}}\text{R(OH)} \end{array} \longrightarrow \begin{array}{l} \text{HC}=\text{CH—CH(OH)} \\ \dot{\text{HC}}=\text{CH—}\ddot{\text{N}}\text{R} \end{array} \longrightarrow \begin{array}{l} \text{HC}=\text{CH—CO} \\ \dot{\text{HC}}=\text{CH—}\ddot{\text{N}}\text{R} \end{array}$$

The dinitrophenylpyridinium chloride obtained by the combination of pyridine with dinitrochlorobenzene is split up by treatment with alkali or with various primary or secondary amines to intensely coloured derivatives of glutaconic aldehyde or its tautomeric forms (A. **330,** 361; **341,** 365; J. pr. Ch. [2], **82,** 1):



$$\begin{array}{l} \text{CH : CH.CH : NC}_6\text{H}_5 \\ \dot{\text{C}}\text{H : CH.NHC}_6\text{H}_5\text{,HCl} \end{array} \xleftarrow{\text{C}_6\text{H}_5\text{NH}_2} \begin{array}{l} \text{CH : CH.CH} \\ \dot{\text{C}}\text{H : CH.}\ddot{\text{N}}\!\left\langle\begin{array}{l}\text{Cl}\\ \text{C}_6\text{H}_3(\text{NO}_2)_2\end{array}\right. \end{array} \xrightarrow{\text{NaOH}} \begin{array}{l} \text{CH : CH.CHO} \\ \dot{\text{C}}\text{H:CH.NHC}_6\text{H}_3(\text{NO}_2)_2 \end{array}$$

Similar behaviour is shown by the addition products of cyanogen bromide, diphenyl-oxalimide chloride, PCl_5, etc., to pyridine (J. pr. Ch. [2], **69,** 105; **70,** 19; **83,** 97, 325). Compare the reversed synthesis of pyridine from derivatives of glutaconic aldehyde.

3. When the alkyl pyridinium iodides are heated to 300° alkyl pyridines result, with a migration of the alkyl-group to α- or γ-C-atom (Ladenburg, B. **17,** 772). This is analogous to the production of homologous anilines from *N*-alkyl anilines.

4. Methyl groups in the α-position and some in the γ-position are able, in contrast with the alkyl groups in the β-position, to condense with aldehydes, such as formaldehyde, chloral, benzaldehyde, like the aldol condensation. The *alkines* thus produced often split off water, forming unsaturated pyridines (*stilbazolene*) (B. **34,** 2223); phthalic acid anhydride and imide behave in this respect like aldehyde (B. **38,** 2806).

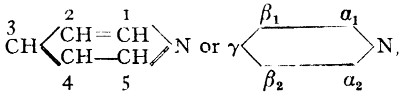
5. Oxidizing agents—*e.g.*, nitric acid, chromic acid—as a rule do not attack the pyridines. All the homologous pyridines, on the other hand, and even the phenyl pyridines, are oxidized by potassium permanganate to *pyridinecarboxylic acids*, which finally yield pyridine upon distillation with lime.

In this connection it is noteworthy that although the phenyl- and benzyl-pyridines yield pyridinecarboxylic acids with permanganate in acid solution, they are oxidized mainly to benzoic acid in alkaline solution (B. **37,** 1373).

6. Reducing agents (sodium and alcohol) convert the pyridine bases into *hexahydropyridines*, or piperidines, which can be decomposed by various methods into fatty bodies (compare piperidine decompositions). The pyridines are reduced to *paraffins* when heated with hydriodic acid. Pyridine yields pentane.

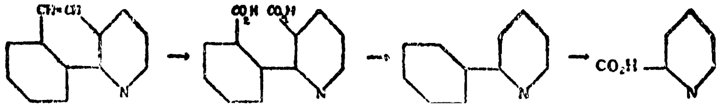
7. *Halogen, nitro-*, and *sulpho*-derivatives are prepared with far more difficulty from the pyridines than from the benzenes.

Isomerides.—The isomerism of the derivatives produced by the replacement of the hydrogen atoms in pyridine can easily be deduced from the given structural formulæ, and is perfectly analogous to the isomerism of the benzene derivatives. Representing the five hydrogen atoms of the pyridine nucleus, with numbers or letters corresponding to the diagram:



then the positions 1 and 5, also 2 and 4 (as in benzene), are similar. The first may be designated the ortho-, the latter the meta-positions; while the position 3, occurring only once, corresponds to the *para* of benzene. From this we conclude that the mono-derivatives of pyridine, $C_5H_4(X)N$, can exist in three series, while six isomerides are possible with the di-derivatives, $C_5H_3(X_2)N$. This is verified by the existence of three methyl-, three propyl- and phenyl-pyridines, $C_5H_4(R)N$, of three pyridine-mono-carboxylic acids, $C_5H_4(CO_2H)N$, of six dicarboxylic acids, etc. The orientation of substituents in pyridine derivatives usually follows from their conversion into carboxylic acids of pyridine.

Constitution of the Pyridine Monocarboxylic Acids.—The constitution of pyridine-α-carboxylic acid or picolinic acid and pyridine-β-carboxylic acid or nicotinic acid is evident from its production in the oxidation of α- and β-phenylpyridines. These latter bodies have been obtained from α- and β-naphthoquinoline. When these are oxidized, the first products are α- and β-phenylpyridinedicarboxylic acids, which upon the loss of $2CO_2$ become phenylpyridines. This proof of constitution presupposes, therefore, the constitution of α- and β-naphthoquinolines. The diagram represents the derivation of the constitution of picolinic acid:

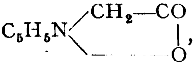


α-Naphthoquinoline. α-Phenylpyridine-dicarboxylic Acid. α-Phenylpyridine. Pyridine-α-carboxylic Acid, α-Picolinic Acid.

The behaviour of the pyridine dicarboxylic acids leads to a simpler deduction of the position of their atoms (B. **18,** 2967). Quinolinic acid (pyridine dicarboxylic acid), formed by the oxidation of quinoline, has the position (1,2), and cinchomeronic acid, from *iso*quinoline, has the position (2,3). Quinolinic acid loses one molecule of carbon dioxide when heated, and forms nicotinic acid, while cinchomeronic acid yields nicotinic acid and *iso*nicotinic acid; therefore nicotinic acid has COOH in the β-position and *iso*nicotinic acid in the γ.

Pyridine, C_5H_5N, boiling at 114·8°, with sp. gr. 1·003 (0°), can be prepared from bone oil, and is obtained from all the pyridinecarboxylic acids on distillation with lime. Its hydrochloride, $C_5H_5N.HCl$, is deliquescent, and with platinum chloride it forms a double salt, $(C_5H_5N.HCl)_2PtCl_4$, melting at 240°. See B. **29,** R. 295, for pyridine mercury compounds. Its *iodomethylate* melts at 117° (B. **29,** R. 994).

Pyridine combines with several other alkyl haloids, as well as acetonyl chloride and phenacyl bromide to form the compounds $C_4H_5N\text{-}(Cl)CH_2COCH_3$ and $C_4H_5.N(Br)CH_2COC_6H_5$ (C. 1899, I. 116; 1900, II. 581). Phosgene unites with 2 mols. pyridine to form *carboxyldipyridinium chloride,* $[C_5H_5N(Cl)]_2CO$ (C. 1900, II. 460); on the addition of acid chlorides by pyridine, see B. **26,** R. 54; Gaz. chim. ital. **39,** II. 445.

Pyridine betaïne,  $C_5H_5N\left\langle\begin{array}{l} CH_2-CO \\ \qquad\quad\ | \\ \text{———}O \end{array}\right.$, m.p. 150° with dec., is formed from pyridine and chloracetic acid (B. **23,** 2609). On the addition products of dinitro-chlorobenzene, cyanogen bromide, etc., with pyridine, and their splitting up to derivatives of glutaconic aldehyde, see above.

Reduced with Na and alcohol, pyridine gives piperidine. Heated with HI it gives normal pentane.

On the product of the addition of sodium bisulphite to pyridine, see B. **41,** 1346; **44,** 2939.

1. **Homologous Pyridines.—Methylpyridines,** $C_5H_4(CH_3)N$, **Picolines** (from *pix*, tar, because they were obtained from coal-tar):

α-**Picoline** boils at 130°; its sp. gr. is 0·949 at 15°, and it is oxidized by potassium permanganate to picolinic acid. β-**Picoline** boils at 143°; its sp. gr. is 0·901. It is formed when strychnine is distilled (B. **28,** 3555), and upon heating glycerol with P_2O_5 and ammonium phosphate; also by heating trimethylenediamine hydrochloride (B. **23,** 2730). It yields nicotinic acid on oxidation. γ-**Picoline** boils at 144°. Its sp. gr. is 0·957 at 15°. It has also been prepared by heating pyridine iodomethylate. It yields *iso*nicotinic acid when it is oxidized.

Dimethylpyridines, *Lutidines,* $C_5(CH_3)_2H_3N$.—Bone oil contains mainly $\alpha\alpha_1$-*Lutidine,* boiling at 142°, with sp. gr. 0·942; α,γ-*Lutidine,* boiling at 157°, with sp. gr. 0·9493; and β,γ-*Lutidine,* boiling at 164° (B. **21,** 1006; **29,** 2996), also found in Scottish shale oil. β,β_1-*Lutidine,* form the corresponding carboxylic acid, boils at 170° (B. **23,** 1113). Found in coal-tar besides $\alpha\beta_1$-lutidine, b.p. 160° (B. **37,** 2062).

α-**Ethylpyridine,** $C_5H_4(C_2H_5)N$, boils at 148°; its sp. gr. is 0·949 at 0°. γ-**Ethylpyridine** boils at 165°; its sp. gr. is 0·952 at 0°. These two compounds result upon heating pyridine ethyl iodide. β-**Ethylpyridine** has been obtained, together with the γ-body, from cinchonine and brucine on heating with caustic potash. It boils at 166°.

Sym. (1,3,5) *Trimethylpyridine,* $C_5H_2(CH_3)_3N$, collidine, is obtained from synthetic dihydrocollidine dicarboxylic ester by oxidation, saponification, and the elimination of carbon dioxide. It boils at 172°. $\alpha\beta'\gamma$-**Collidine,** boiling at 165°–168°, occurs in coal-tar (B. **29,** 2998). $\alpha\beta\gamma$-**Trimethylpyridine,** b.p. 185°–188°, on oxidation gives carbocinchomeronic acid (C. 1900, I. 1161).

$\alpha\beta'$-**Methylethylpyridine,** $C_5H_3(CH_3)(C_2H_5)N$, has been prepared from various aldehyde compounds, hence called *aldehydine* or *aldehydecollidine.* It boils at 178°. $\alpha\alpha'$-**Methylethylpyridine,** b.p. 160°, from methylol-$\alpha\alpha_1$-lutidine by reduction (B. **42,** 137). $\beta\gamma$-**Methylethylpyridine,** β-collidine, b.p. 190°–200°, with β-ethyl pyridine from cinchonine by distillation with potash (B. **35,** 1351).

α-**Propylpyridine, Conyrine,** $C_5(C_3H_7)H_4N$, is produced on heating coniine with zinc-dust. It boils at 167°.

α-*iso***Propylpyridine** is produced, together with the γ-compound, when pyridine propyl iodide or *iso*propyl iodide is heated. It boils at 158°.

Parvoline, *v*-**Tetramethylpyridine,** boiling at 227°–230°, occurs in coal-tar (B. **28,** 796).

α- and γ-**Benzylpyridine,** $C_5H_4N(CH_2C_6H_5)$, b.p. 276° and 287°, from pyridine chloro- or iodo-benzylate at 270°, besides a small quantity of β-**benzylpyridine,** m.p. 34°, b.p. 287°, which is better obtained by reduction with HI and phosphorus (B. **36,** 2711). The iodomethylates of α- and γ-benzylpyridine, treated with NaHO, yield, instead of the pyridones, α- and γ-**benzylidene-***N***-methyldihydropyridines,** from which the pyridinium salts can be regenerated by means of acids (B. **38,** 2496).

β,β_1-**Dibenzylpyridine,** $C_5H_3(C_7H_7)_2N$, boiling at 89°, is formed in the condensation of benzaldehyde with benzoyl piperidine (A. **280,** 36).

α- and β-**Phenylpyridine,** $C_5(C_6H_5)H_4N$, boiling at 269° and 270°, result from the elimination of $2CO_2$ from their carboxylic acids, the decomposition products of α- and β-naphthoquinoline. The α-body can also be made by heating the corresponding α-pyridone with zinc dust (B. **29,** 1678). β-Phenyl-pyridine is also formed by the distillation of *N*-benzyl-pyrrole through feebly incandescent tubes, and by the action of benzal chloride and Na ethylate upon pyrrole.

p-Nitrophenylpyridine, melting at 117°, is obtained from nitrosodiazobenzene and pyridine. By reduction it yields *p*-aminophenyl-pyridine, melting at 102°, which yields α-phenylpyridine (B. **29,** 167). **Dinitrophenylpyridine** melts at 118° (B. **29,** 279). γ-**Phenylpyridine,** melting at 77° and boiling at 274°, results from a transposition of the condensation product of acetoacetic ester with benzaldehyde and ammonia; a mixture of α- and γ-phenylpyridine is also formed by the action of benzene diazonium salts upon pyridine (compare B. **37,** 1370).

α,α_1-**Phenylmethylpyridine,** $C_5(C_6H_5)(CH_3)H_3N$, boiling at 281°, is obtained from cinnamylidene acetoxime (B. **28,** 1727). α,α_1-**Diphenyl pyridine,** melting at 82°, has been obtained (1) by distilling the oxime of cinnamylene-acetophenone (method 3); (2) from α,α_1-diphenyl-γ-pyridinecarboxylic acid, produced on heating diphenacyl-malonic acid with ammonia; and (3) by oxidizing α-phenyl-naphthocinchonic acid (B. **29,** 798; **30,** 1499).

$\alpha\alpha'\gamma$-**Triphenylpyridine,** m.p. 137°, $\alpha\alpha'\beta\beta'$- and $\alpha\alpha'\beta\gamma$-**Tetraphenylpyridine,** m.p. 179° and 233°, and **pentaphenylpyridine,** m.p. 179° and 240°, are formed from benzal-diacetophenone, αγ-dibenzoyl-diphenyl-propane, desoxy-benzoin benzylidene acetophenone, and benzamarone with hydroxylamine (method 3; compare A. **302,** 233, 240; **303,** 225).

γγ-**Dipyridyl,** $(C_5H_4N)_2 + 2H_2O$, m.p. 73° (114°), b.p. 305°, is formed from pyridine by the action of sodium, besides an oily polymeric pyridine (C_5H_5N) (B. **24,** 1478). Similarly, on heating $\alpha\alpha_1$-lutidine a **tetramethyl-dipyridyl,** $[C_5H_2(CH_3)_2N]_2$, m.p. 149°, is formed. This on oxidation yields a dipyridyl tetracarboxylic acid, which on eliminating CO_2 passes into γγ-dipyridyl (B. **32,** 2209).

ββ-**Dipyridyl,** m.p. 68°, b.p. 287°, from its dicarboxylic acid, an oxidation product of phenanthroline. On a further dipyridyl, see B. **21,** 1077.

Vinylpyridine, $C_5H_4(C_2H_3)N$, results when pyridine vapours are conducted, together with ethylene, through a tube heated to redness, as well as from α-picolyl alkine by the loss of water, and from pyridyl-β-brompropionic acid by the exit of CO_2 and HBr. It boils at 160° (B. **20,** 1644; A. **265,** 229).

α-**Propenylpyridine,** $(C_5H_4N)CH:CHCH_3$, b.p. 290°, usually called allylpyridine, is formed from α-picoline and paraldehyde on heating to 260° (A. **247,** 26); on reduction with Na and alcohol it yields propylpiperidine or inactive coniine.

γ-**Propenyl-pyridine,** b.p. 201°, from γ-picoline and paraldehyde (B. **38,** 157). α-**Styryl-pyridine,** Stilbazole, $C_5(CH:CHC_6H_5)H_4N$, m.p. 61°, b.p. 325°, by heating α-picoline with benzaldehyde and $ZnCl_2$; benzaldehyde and its substitution products react similarly with other α-methylated pyridines, like $\alpha\alpha_1$-methyl-phenyl-pyridine, α,γ-lutidine. $\alpha\alpha_1$-Lutidine gives $\alpha\alpha_1$-Distyrylpyridines, $ArCH:CH(C_5H_3N)CH:CHAr$ (B. **33,** 3494; **34,** 464, 1893; **35,** 2774, 2790; **36,** 118, 119, 1683). γ-**Styrylpyridine,** m.p. 217°, from γ-Picoline (B. **38,** 2837).

2. **Halogen Pyridines.**—The pyridines containing halogens in the nucleus are obtained with difficulty by the direct action of the halogens upon the pyridines. Bromine particularly replaces the alkyl group in the homologous pyridines very easily (B. **25,** 2985; **28,** 1759). The replacement of the pyridine hydrogen atoms is more easily effected upon

heating pyridine or the hydroxypyridines with phosphorus or antimony pentachlorides.

By heating pyridine with PCl_5 to 210° to 220° one obtains $\alpha\alpha_1$-**dichloro-pyridine,** m.p. 88° (also obtained from dichlor*iso*-nicotinic acid by eliminating CO_2); also three **trichloro-pyridines,** melting at 50°, 68°, and 72° respectively; *αα′ββ′-*, *αββ′γ-*, and *αα′βγ*-**tetrachloro-pyridines,** melting at 91°, 22°, and 75° respectively; and as a chief product **pentachloro-pyridine,** C_5Cl_5N, m.p. 125°, also produced from dioxy-pyridine or glutaconimide with PCl_5, and, besides lower chlorination products, by prolonged action of chlorine upon pyridine hydrochloride. By heating with alcoholic ammonia several of the higher chlorinated pyridines have been converted into aminochloropyridines (C. 1898, II. 349; 1899, II. 1055; 1900, I. 135, 350, 552, 818; II. 110, 482; J. pr. Ch. [2], **83,** 106).

On the chlorination of α-picoline, see C. 1909, I. 382.

α-**Chloropyridine,** b.p. 166°, is prepared from α-hydroxy-pyridine, or better from *N*-alkyl pyridones, with PCl_5; similarly, the *N*-alkyl pyridones with $POBr_3 + PBr_5$ yield α-**bromo-pyridine,** b.p. 193°. On treating chloropyridine with methyl-iodide, α-**iodopyridine-iodo-methylate,** $C_5H_4IN(CH_3)I$, is formed (B. **32,** 1297). β-**Chloro-** and β-**bromo-pyridine,** b.p. 148° and 170°, are obtained from potassium pyrrole with $CHCl_3$ and $CHBr_3$ respectively; β-chloro-pyridine also from α-chloro-glutaconic aldehyde and NH_3 (B. **38,** 1651). Homologous β-halogen pyridines (see C. 1900, I. 817). α-**Phenyl-**α_1-**chloropyridine,** m.p. 34°, from phenyl pyridine (see B. **29,** 1679). γ-**Chlorolutidine,** $C_5(CH_3)_2H_2ClN$, b.p. 176°–178°, from lutidone (A. **331,** 254).

3. *Pyridine Sulphonic Acids.*—β-**Pyridine sulphonic acid,** $C_5H_4(SO_3H)N$, is formed from pyridine with fuming sulphuric acid. Its sodium salt, on distillation with CNK, yields β-cyano-pyridine, the nitrile of nicotinic acid, and on fusing with potash, β-hydroxypyridine.

α-**Pyridine sulphonic acid,** m.p. 240°, and **lutidine-γ-sulphonic acid** are prepared by oxidizing the corresponding mercaptans (B. **33,** 1556). Heating piperidine with sulphuric acid produces pyridine and pyridine sulphonic acids.

4. *Nitro-pyridines.*—Nitration of the pyridine nucleus seems only possible when NH_2-, OH-, or similar groups are present, which, as in the case of benzene, facilitate the nitration.

The nitration of β-hydroxypyridine in the form of its acetyl ester with nitric acid containing N_2O_3 gives rise to two **nitro-hydroxypyridines,** melting at 211° and at 295°–298° with decomposition; also a **dinitro-hydroxypyridine** melting at 133° (B. **28,** R. 911). See nicotinic acid for the **nitro-aminonicotinic acids.**

5. *Amino-* and *Hydrazino-pyridines* are obtainable from α- and γ- (not β-) halogen pyridines by the action of NH_3. Amino-pyridines are also obtained from the pyridinecarboxylic acids (1) by the action of KOBr upon their amides (Hofmann's reaction) (C. 1902, II. 647); or (2) by transforming the acid azides with alcohol into pyridyl-urethanes and splitting up the latter (Curtius's reaction). The closest analogy to the anilines is presented by the pyridines aminated in the β-position, since they can be transformed into diazo- and diazoamino-compounds and into azo-dyestuffs.

α-Aminopyridine, m.p. 56°, b.p. 204°, from α-chloropyridine with ammoniated zinc chloride at 220°; from α- or α_1-amino-nicotinic acid by elimination of CO_2; and from α-picolinic acid amide (B. **27,** R. 410; A. **288,** 253; B. **32,** 1301). **α-Anilinopyridine,** m.p. 108°, from chloropyridine and aniline zinc chloride (B. **35,** 3674). **β-Aminopyridine,** m.p. 64°, b.p. 251°, from nicotinic acid amide with KOBr (B. **28,** R. 322); also by breaking up *β-pyridyl urethane,* $(C_5H_4N)NHCO_2C_2H_5$, m.p. 87°, or dipyridyl urea, obtained from nicotinic acid azide with alcohol or water (B. **31,** 2493). Diazo-pyridine salts, *β-diazo-amino-pyridine,* $(C_5H_4N)N:N.NH(C_5H_4N)$, pyridine azo-resorcin (see B. **31,** 2495). **$\beta\beta_1$-Diamino-$\alpha\alpha_1$-lutidine,** $C_5(CH_3)_2(NH_2)_2HN$, m.p. 170°, from lutidine dicarboxylic acid diazide, etc. (B. **33,** 1114).

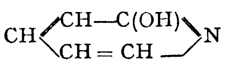
γ-Aminopyridine, m.p. 155°, from *iso*nicotinic acid amide (C. 1902, II. 648).

γ-Amino-$\alpha\alpha_1$-lutidine, m.p. 186°, b.p. 246°, from amino-lutidine carboxylic acid.

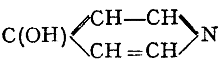
γ-Lutidylhydrazine, $C_5(CH_3)_2(NHNH_2)H_2N$, m.p. 116°, from γ-chlorolutidine with hydrazine hydrate at 150°. Chlorolutidine with phenylhydrazine gives γ-**phenylhydrazinolutidine,** $C_6H_5NHNH(C_7H_8N)$, which on oxidation yields **benzeneazolutidine,** $C_6H_5N:N(C_7H_8N)$, m.p. 63° (B. **36,** 1111). For chlorinated amino-pyridines, see preceding page.

6. *Hydroxypyridines.*—The hydroxypyridines correspond to the amino-phenols, in that they form salts with bases and acids. They are formed with special ease from the hydroxypyridine carboxylic acids by the elimination of the carboxyl groups. Most of these acids have been produced by the action of ammonia upon the corresponding pyrone derivatives. Ferric chloride imparts a red colour to nearly all their solutions. On the other hand, the α- and γ-hydroxypyridines manifest the deportment of cyclic imides or lactams. They must be viewed as *keto*-compounds of the hydropyridines, and are called, therefore, *pyridones.* The following formulæ have been considered for the α- and γ-hydroxypyridines:

I.

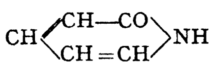


α-Hydroxypyridine.

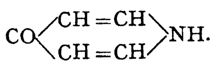


γ-Hydroxypyridine.

II.



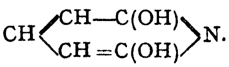
α-Pyridone.



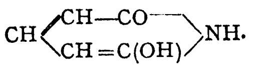
γ-Pyridone.

Although it is undetermined which of the two possible representations belongs to the free oxy-bodies, alkyl derivatives are obtained from both in which the alkyl residue replaces the imide or hydroxyl hydrogen (B. **24,** 3144). The following formulæ should also be considered for the α,α_1-dioxypyridines or glutaconimides:

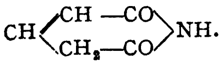
I.



II.



III.

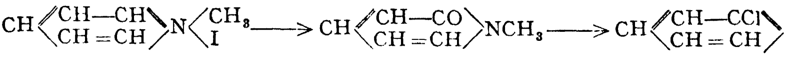


(Compare the pyrazolones, the isoxazolones, benzimidazolones, indoxyl, isatin, etc.)

The transformations of the *N*-alkyl pyridones resemble those of the antipyrines, yielding with PCl_5 the halogen alkylates of the *a*- and *γ*-chloro-pyridines. The latter with NaHO regenerate the *N*-alkyl pyridones, and with potassium sulphydrate and selenide they yield *N*-alkyl thio- and -seleno-pyridones respectively. This is why, in the case of the antipyrines as well as the *N*-alkyl pyridones, the existence of a linkage-atom of oxygen has been supposed, making up the group $\overset{\|}{\underset{|}{\mathrm{RN}}}\mathrm{-O-}\overset{\|}{\underset{|}{\mathrm{C}}}$ (compare A. **331,** 245; B. **36,** 1062).

(1) *Monoxypyridines.*—*a*-**Hydroxypyridine,** *a*-**Pyridone,** C_5H_5ON, melting at 106° and boiling at 281°, is obtained from hydroxyquinolinic acid and from hydroxynicotinic acid. Bromine water converts it into a dibromhydroxypyridine, $C_5H_2Br_2(OH)N$, melting at 206°. With ethyl iodide it yields N-*ethyl-a-pyridone,* $\mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}CO}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{N.C_2H_5}$, boiling at 247°, while the silver salt and the same reagent yield *a-ethoxy-pyridine,* $\mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}C(OC_2H_5)}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{N}$, boiling at 156°. *a-Methoxypyridine* can also be prepared from *a*-pyridone and diazomethane (B. **28,** 1625).

N-Alkyl-*a*-pyridones are formed in general from the halogen alkylates of the *a*-chloropyridines with NaHO (see above), and from pyridine halogen alkylates by the action of NaHO and potassium ferricyanide (J. pr. Ch. [2], **84,** 435). By heating with phosphorus halides the *N*-alkyl pyridones are transformed into *a*-halogen pyridines with elimination of halogen alkyl (B. **32,** 1297):



$$\mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}CH}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{N}\left\langle\begin{matrix}\mathrm{CH_3}\\ \mathrm{I}\end{matrix}\right. \longrightarrow \mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}CO}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{NCH_3} \longrightarrow \mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}CCl}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle$$

1,3-**Dimethyl-*a*-pyridone,** *pseudo-lutido-styril, mesitene lactam,* m.p. 180°, is formed from dimethylcoumalin or mesitene lactone with NH_3, and from its carboxylic acids; on nitration it is converted into a nitro-*pseudo*-lutido-styril, which can be reduced to amino-*pseudo*-lutido-styril, $C_5(CH_3)_2(OH)(NH_2)HN$, m.p. 205° (C. 1898, I. 848). *a*-**Phenyl-*a*$_1$-pyridone,** m.p. 197°, from phenylcoumalin with ammonium acetate; aniline gives *N*a_1-**diphenyl-*a*$_1$-pyridone,** m.p. 145° (B. **29,** 1677).

β-**Hydroxypyridine,** $C_5H_4(OH)N$, melting at 124°, distils without decomposition. It is produced when *β*-pyridine sulphonic acid is fused with caustic potash (B. **28,** R. 911), or by the action of nitrous acid upon *β*-aminopyridine. Its ethyl ether, $C_5H_4(OC_2H_5)N$, results from the interaction of *β*-brompyridine and alcoholic potash.

γ-**Hydroxypyridine,** *γ*-**Pyridone,** $C_5H_5ON(+H_2O)$, melting at 148°, is produced by heating hydroxypicolinic acid and chelidamic acid. Methyl iodide converts it into the hydroiodide of *N*-methyl-*γ*-pyridone, $\mathrm{OC}<\begin{matrix}\mathrm{CH{-}CH}\\ \mathrm{CH{=}CH}\end{matrix}>\mathrm{NCH_3}$, melting at 89°. With diazo-methane it yields a mixture of *N*-methyl-*γ*-pyridone, and *γ-methoxy-pyridine,* $\mathrm{(CH_3O)C}\left\langle\begin{matrix}\mathrm{CH{-}CH}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{N}$ (C. 1906, I. 1439). This compound may be prepared by heating *γ*-chlorpyridine with sodium ethylate. It boils at 190°, and, unlike its isomeride, is broken down when heated with hydriodic acid into methyl iodide and *γ*-pyridone.

αα′-**Dimethyl-*γ*-oxypyridine, *γ*-Lutidone,** $C_5(CH_3)_2H_3ON(+1\frac{1}{2}H_2O)$, melting at 225°, is obtained from lutidone dicarboxylic acid (p. 179), as well as from dehydracetic acid on heating with ammonia (B. **28,** R. 644). With phenylhydrazine, *γ*-lutidone yields a phenylhydrazone, $(C_7H_9N)NNHC_6H_5$, m.p. 125° (J. pr. Ch. [2], **64,** 496). *N*-**Methyl-*γ*-lutidone** is also formed from *γ*-chlorolutidine iodo-methylate with dilute NaHO (A. **331,** 256). *γ*-**Ethoxylutidine,** boiling at 207°, results upon diazotizing *γ*-aminolutidine in alcoholic solution (B. **27,** 1328). For nitro- and amino-lutidone, see C. 1898, I. 1124.

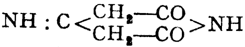
(2) *Dioxypyridines.*—*αα′*-**Dihydroxypyridine,** *glutaconimide,* $C_5H_5O_2N$ (I. 520), melting at 183°–184°, is obtained from oxyglutarimide, glutaconamic acid, or glutacondiamide. Its salts (*chloride,* + H_2O; *sulphate,* + $2H_2O$) are decomposed by much water. It yields pyridine upon distillation with zinc dust. Phosphorus penta-chloride converts it into pentachloro-pyridine.

αβ′-**Dihydroxypyridine,** m.p. 248°, distinguished by its blue coloration with ferric chloride, is obtained from *β*-oxypyridine by soda fusion; by oxidation with MnO_2 and sulphuric acid it forms a pyridine quinone, $C_5H_3O_2N$ (C. 1898, I. 250).

Several isomeric dioxy-pyridines have been obtained by fusing pyridine disulphonic acids with potash (B. **17,** 1832), from comenaminic acid or dioxy-picolinic acid (B. **18,** R. 633) by elimination of CO_2, etc.

β-**Methyl-*αα′*-dihydroxypyridine,** $C_5(CH_3)H_4O_2N$, melting at 191°, *β*-**Ethyl-,** *β*-**Benzyl-dihydroxypyridine,** etc., have been prepared by the action of ammonia upon methyl-, ethyl-, and benzyl-glutaconic esters (B. **26,** R. 318, 587). These dioxypyridines correspond to resorcinol of the benzene series, and like it they form *dyes* with phthalic anhydride (see B. **26,** 1559).

αγ-**Dihydroxypicoline,** m.p. 331°, is obtained from the synthetic dihydroxypicoline carboxylic acid. With N_2O_3 it yields a nitrosodihydroxypicoline, which on treatment with stannous chloride and HCl gives a trihydroxypicoline, m.p. 264° (B. **32,** 1985; compare C. 1897, II. 490).

(3) *Trioxypyridines.*—*αα′γ*-**Trihydroxypyridine,** *Triketopiperidine,* $C_5H_5O_3N$, decomposes at 220° to 230°. It corresponds to phloroglucin. It can be obtained by boiling glutazine with hydrochloric acid. Heated with ammonia it reforms **Glutazine,** *β-Imino-glutarimide,*  $NH:C\!<\!\begin{matrix}CH_2—CO\\CH_2—CO\end{matrix}\!>\!NH(?)$, melting with decomposition at 300°, which may be prepared by heating acetone dicarboxylic ester with ammonia (B. **20,** 2655).

Pyro-mecazonic Acid is an isomeric trihydroxypyridine obtained from pyromeconic acid with ammonia. Ferric chloride colours it a dark indigo blue.

7. *Thiopyridines.*—Mercaptans of the pyridine series are prepared, like the amines, from *α*- or *γ*-halogen pyridines with alcoholic KSH solution (B. **33,** 1556); *α*-**pyridyl mercaptan,** thio-pyridone, C_5H_5SN, yellow prisms, m.p. 125°, from *α*-chloropyridine, gives with iodine a bisulphide, $(C_5H_4N)_2S_2$, m.p. 58°; with nitric acid pyridinesulphonic acid; with methyl iodide **methyl *α*-pyridyl sulphide,** b.p. 197°; the latter is also formed by distillation from the iodomethylate of *N*-**methyl thio-pyridone,** $C_5H_4SN(CH_3)$, m.p. 90°; *N*-methylthiopyridone is

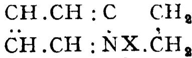
obtained from *N*-methyl-*α*-pyridone with P_2S_5, and from iodo-pyridine iodo-methylate with KSH (see above). With potassium selenide the iodo-pyridine iodo-methylate yields ***N*-methyl-*α*-seleno-pyridone,** $C_5H_4SeN(CH_3)$, m.p. 80°, the iodo-methylate of which gives rise to **methyl-*α*-pyridyl-selenide,** $(C_5H_4N)SeCH_3$, b.p. 212°, on distillation (A. **331,** 245).

***αα*₁-Lutidyl-*γ*-mercaptan** *thio-lutidone,* $C_5(CH_3)_2H_3SN$, m.p. 224°, from *γ*-chloro-lutidine; lutidyl-sulphide, $(C_7H_8N)_2S$, m.p. 83°; bisulphide, m.p. 57°; with alkaline H_2O_2 solution lutidine-*γ*-sulphonic acid is obtained. *N*-Methyl-thio-lutidone, $C_5(CH_3)_2H_2SN(CH_3)$, m.p. 268°, from *γ*-chloro-lutidine iodo-methylate with KSH, gives with methyl iodide the iodo-methylate of methyl-*γ*-lutidyl sulphide, $(C_7H_8N)SCH_3$, m.p. 51°, b.p. 233°; by oxidation with chlorine water the *N*-methyl thio-lutidone gives a trioxide, $C_7H_8N(CH_3)SO_3$ (A. **331,** 245).

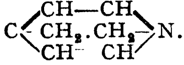
8. **Pyridyl Alcohols.**—These are sometimes called *pyridyl alkines.* They arise (1) in the aldol condensation of *α*-methyl pyridines with aldehydes on boiling with water; (2) from their HBr-esters, the homologous pyridines brominated in the side-chain; (3) by the reduction of the corresponding ketones.

***β*-Pyridylcarbinol,** $C_5H_4N[\beta]CH_2OH$, is obtained from its bromide, which results from the treatment of *β*-picoline with bromine at 150° (B. **33,** 3498); similarly, ***β′α*-picolyl-methylcarbinol,** $C_5H_3(CH_3)NCH(OH)CH_3$, b.p. 240°, is obtained from bromo-collidine on boiling with water (B. **28,** 1759).

***α*-Pyridyl-ethyl-carbinol,** $C_5H_4N\,[\alpha]\,CH(OH)C_2H_5$, b.p. 213°–218°, *α*- and ***γ*-pyridyl-phenyl-carbinol,** $C_5H_4N.CH(OH)C_6H_5$, m.p. 82° and 126°, are obtained by the reduction of *α*-pyridyl ethyl ketone and *α*- and *γ*-pyridyl phenyl ketone respectively with Na amalgam (B. **37,** 1370). ***α*-Pyridyl-dimethylcarbinol,** $C_5H_4N.C(OH)(CH_3)_2$, m.p. 51°, b.p. 204°, and ***α*-pyridyl-diethylcarbinol,** b.p.$_{24}$ 153°, result from picolinic acid esters and alkyl magnesium haloids (B. **41,** 4103).

From *α*- and *γ*-alkylated pyridines with aldehydes the following alkines are obtained (B. **22,** 2538; **23,** 2709; **34,** 2233; **35,** 1343; **36,** 2904; **37,** 737; **39,** 1045; **42,** 132; A. **301,** 124): **Methylol-*α*-picoline,** *Picolylalkine,* $(C_5H_4N)\alpha\text{-}CH_2CH_2.OH$, b.p.$_9$ 115°, besides **Dimethylol-*α*-picoline,** $(C_5H_4N)\alpha\text{-}CH(CH_2.OH)_2$, m.p. 78°, and **Trimethylol-*α*-picoline,** $(C_5H_4N)\alpha\text{-}C(CH_2OH)_3$, m.p. 68°, on heating *α*-picoline with formaldehyde. Methylol-*α*-picoline heated with HBr and HI respectively gives ***α*-bromo-** and **iodo-ethyl-pyridine,** $C_5H_4N\text{-}\alpha\text{-}CH_2CH_2X$, unstable oils which easily transpose into the cyclic pyridinium salts,  $\begin{array}{l} CH.CH:C\quad CH_2 \\ \dot{\dot{C}}H.CH:\dot{N}X.\dot{C}H_2 \end{array}$, m.p. 213° and 227°, of high melting-point, and are transformed with NH_3 and amines to ***α*-pyrid-ethylamine,** $(C_5H_4N)\alpha\text{-}CH_2CH_2NH_2$, b.p.$_{12}$ 91° (B. **37,** 161; **38,** 3329).

From *γ*-picoline and formaldehyde we obtain **Methylol-*γ*-picoline,** $(C_5H_4N)\gamma\text{-}CH_2.CH_2OH$, b.p.$_{15}$ 126°, and **Trimethylol-*γ*-picoline,** $(C_5H_4N)\gamma\text{-}C(CH_2OH)_3$, m.p. 156°–157°; from *αα*₁-lutidine **Methylol-** and **Dimethylol-lutidine,** m.p. 55° and 74°; from *β*-collidine, ***γ*-Dimethylol-collidine,** $[C_5H_3(C_2H_5)N]\gamma\text{-}CH(CH_2OH)_2$, m.p. 103°; from *α*-ethyl-pyridine, **Methylol-*α*-ethylpyridine,** $(C_5H_4N)\alpha\text{-}CH(CH_3)CH_2OH$.

The iodide obtained from methylol-γ-picoline with HI, like the α-iodo-ethyl pyridine, is transformed on heating into a dicyclic pyridinium salt, 
$\mathrm{C}\left\langle\begin{array}{c}\mathrm{CH{-}CH}\\ \mathrm{CH_2.CH_2}\\ \mathrm{CH\quad CH}\end{array}\right\rangle\mathrm{N.J}$. (B. **42,** 124). On reduction with HI and phosphorus or zinc dust, these alkines yield the corresponding alkyl pyridines, and by oxidation pyridine carboxylic acids. **Ethylol-α picoline,** $(C_5H_4N)\alpha\text{-}CH_2CH(OH)CH_3$, m.p. 32°, b.p.$_{20}$ 124°, and **Benzylol-α-picoline,** $(C_5H_4N)\alpha\text{-}CH_2.CH(OH)C_6H_5$, m.p. 97°, from picoline with acetaldehyde and benzaldehyde respectively. **Trichlor-ethylol-α-picoline,** m.p. 87°, from α-picoline with chloral.

9. **Pyridyl Ketones.**—Ketones of the pyridine series are obtained in the distillation of pyridine carboxylic acids with fatty or aromatic acids (Engler, B. **24,** 2525), or by ring synthesis (B. **30,** 2295; **31,** 1025). They yield secondary alcohols, together with pinacones, by reduction.

α-Pyridyl methyl ketone, $(CH_3CO)C_5H_4N$, boiling at 192°, is prepared from calcium picolinate and acetate. Its *oxime* melts at 120°. Its *phenylhydrazone* melts at 155°. For condensation products with aromatic aldehydes, see B. **35,** 4061.

β-Pyridyl methyl ketone, boiling at 220°, is obtained from calcium nicotinate and acetate. **α-Picolyl-γ-methyl ketone,** $C_5H_3(CH_3)(COCH_3)N$, boiling at 233°, results upon oxidizing the corresponding alkine (B. **28,** 1764).

α-Pyridyl ethyl ketone, $(C_2H_5CO)C_5H_4N$, boiling at 205°, is changed by sodium and amyl alcohol to *α-ethyl piperyl alkine*, $C_2H_5CH(OH).\text{-}C_5H_9NH$, and further into (*d* + *l*)-coniine.

Phenyl β-pyridyl ketone, $C_6H_5CO.C_5H_4N$, b.p. 307° (B. **20,** 1209), from benzoyl picolinic or *iso*nicotinic acid, gives two isomeric oximes, m.p. 142° and 162° (B. **29,** R. 832). **Phenyl α- and γ-pyridyl ketone,** b.p. 317° and m.p. 72°, b.p. 315° respectively, by oxidation of the benzyl pyridines. **$\beta\beta_1$-Diacetyl-$\alpha\alpha_1$-lutidine,** $C_5H(COCH_3)_2(CH_3)_2N$, m.p. 74°, is obtained from methenyl-bisacetylacetone, $(CH_3CO)_2CH.CH:\text{-}C(COCH_3)_2$, with ammonia, and by oxidation with N_2O_3, from its dihydro-derivative, resulting from methylene bisacetylacetone with NH_3 (B. **30,** 2295; A. **297,** 71). In a similar manner, other pyridyl ketones were obtained from their synthetic dihydro-derivatives—*e.g.*, **γ-phenyl-$\beta\beta_1$-diacetyllutidine,** m.p. 188°, from benzal-acetonylacetone with amino-acetylacetone (B. **31,** 1026).

p-Nitrophenyl α-picolyl ketone, $NO_2C_6H_4COCH_2[\alpha]C_5H_4N$, m.p. 160°, from the corresponding alkine (B. **35,** 1165). **α-Acetacetyl pyridine,** $(C_5H_4N)COCH_2COCH_3$, m.p. 50°, b.p.$_{15}$ 137°–143°, from picolinic acid ester, acetone, and sodium ethylate (B. **29,** R. 846); and from nicotinic and *iso*nicotinic acid ester: **β- and γ-acetacetylpyridine** (M. **22,** 615).

10. *Pyridine Carboxylic Acids.*—These acids of pyridine result upon oxidizing the homologous pyridines with potassium permanganate, when alkyl as well as phenyl groups are converted into carboxyl. The condensed pyridine derivatives—*e.g.*, quinoline, *iso*quinoline, etc.—are similarly decomposed, the benzene rings being ruptured and oxidized to carboxyl. Hence, most alkaloids, being pyridine derivatives, yield these acids upon energetic oxidation.

For the separation of the acids obtained from mixtures of pyridine bases, see B. **33,** 1225, etc.

The lower acids can be prepared from the pyridine polycarboxylic acids by heating them with hydrochloric acid. Usually, in this treatment it is the COOH-groups, occupying the α-position, which are split off. Upon heating with lime all the carboxyl groups are eliminated and pyridine is formed.

The pyridine carboxylic acids, like the other pyridine derivatives, are reduced by sodium and alcohol to piperidine carboxylic acids.

A number of pyridine carboxylic acids are reduced by sodium amalgam in aqueous-alkaline solution to *lactonic acids* of the fatty series. The group $—CH{=}N—CH{=}$ is then converted into $—CO—O—CH_2—$ (B. **25,** R. 904; **26,** R. 8; **27,** R. 193, etc.).

As the pyridines are bases, their acids manifest the character of amino-acids. The basic properties disappear with the polycarboxylic acids. On heating with iodine alkyls in soda solution the pyridine carboxylic acids yield betaïne (B. **36,** 616).

The methods of determining position or place in the monocarboxylic acids have been given on p. 165. Of the dicarboxylic acids, quinolinic acid, because of its formation from quinoline, must be the α,β-dicarboxylic acid, and cinchomeronic acid, because of its production from *iso*quinoline, must be the β,γ-dicarboxylic acid.

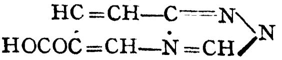
A. *Pyridine-mono-carboxylic Acids:*

α-Pyridinecarboxylic acid, Picolinic acid, $C_5H_4N(CO_2H)$, is obtained by the oxidation of α-picoline. It melts at 135°–136°, and sublimes. Ferrous sulphate imparts to its solutions, as well as to those of all pyridine carboxylic acids having the carboxyl group in the α-position, a *yellow-red* colour.

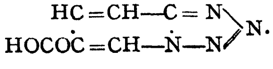
Ethyl ester, b.p. 243°; chloride, m.p. 220°; amide, m.p. 107°; nitrile, m.p. 29°, b.p. 212°–215° (C. 1902, II. 373, 649).

β-Pyridinecarboxylic acid, Nicotinic acid, was first obtained by oxidizing nicotine. It is also prepared from β-picoline, as well as from β-cyanpyridine. It melts at 228°–229°. Its iodomethylate forms a *betaïne,* $C_5H_4(COO)N.CH_3$, which is identical with the alkaloid *trigonelline.* **α′-Chlornicotinic Acid,** melting at 199°, is obtained from hydroxynicotinic acid, and when heated with ammonia becomes **α′-Aminonicotinic Acid,** which changes to α-aminopyridine on heating, and by nitration yields **β′α′-nitroaminonicotinic acid,** melting at 280°. The reduction of the latter yields **β′α′-diaminonicotinic acid. α′-Aminonicotinic Acid,** from quinolinamic acid, also yields α-aminopyridine on the application of heat, and by nitration becomes **nitroaminonicotinic acid** (B. **27,** 1317; A. **288,** 253).

With hydrazine the α′-chloro-nicotinic acid gives **α′-hydrazinonicotinic acid,** $COOH\,[2]\,C_5H_3N\,[5]\,NHNH_2$, m.p. 283°, which, on boiling with formic acid, yields the so-called benzo-triazole carboxylic acid; and with NO_2H benzo-tetrazole carboxylic acid,



and



On oxidation these acids yield triazole and tetrazole respectively (B. **36,** 1111).

γ-**Pyridinecarboxylic acid,** *iso***nicotinic acid,** m.p. 304°, from γ-methyl pyridine or from cinchomeronic acid by elimination of CO_2 (C. 1900, II. 482); chloride, m.p. 270° (C. 1901, I. 1052). Ethyl ester, b.p. 218°, gives by decomposition of its iodo-ethylate iso*nicotinic acid ethyl betaïne,* m.p. 241° with dec.; *amide,* m.p. 155°; *nitrile,* m.p. 79° (C. 1902, II. 649).

Homologous Pyridine Mono-carboxylic Acids.—α-**Methyl-**α_1**-pyridinecarboxylic acid,** $C_5H_3N[\alpha_1\alpha_1](CH_3)CO_2H$, m.p. 85°, from $\alpha\alpha_1$-lutidine (B. **33,** 1081, 1230); γ-**methyl-**α-**pyridinecarboxylic acid,** capable of sublimation, is formed from uvitoninic acid (see below) by elimination of CO_2. γ-**Methylnicotinic acid,** m.p. 210°, from γ-methylquinolinic acid on rejection of CO_2, condenses with formaldehyde to the dioxylactone, $\overline{\mathrm{OCH_2C(CH_2OH)_2[3]C_5H_3N[2]C}}\mathrm{O}$ (B. **34,** 4336). αγ-**Dimethylnicotinic acid,** $C_5(CH_3)_2H_2N.CO_2H(+2H_2O)$, is formed as an ester from aceto-acetic acid with 2 mols. acetaldehyde and NH_3 by method (2). γ-**Chloro-**α′β-**dimethylnicotinic acid,** $C_5HCl(CH_3)_2N[\beta]CO_2H$, m.p. 168° to 170°, results from β-aminocrotonic acid ester (Vol. I.) by heating with $POCl_3$. It is transformed, with hydrazine and phenyl hydrazine, to hydrazine derivatives, which yield bicyclic pyrazolones with elimination of H_2O (B. **36,** 515; A. **366,** 324).

$\alpha\alpha_1$-**Diphenyl-**γ-**pyridinecarboxylic acid,** m.p. 279°, from diphenacyl-acetic acid with NH_3 (C. 1903, I. 1362).

B. *Pyridine Dicarboxylic Acids:*

αβ-**Pyridinedicarboxylic acid, Quinolinic acid,** $C_5H_3N(COOH)_2$, melting at 190° with decomposition, is obtained from quinoline and from α- and β-methyl-quinoline by oxidation with potassium permanganate (B. **19,** 293). The oxidation of *p*-hydroxyquinoline with bleaching lime yields an intermediate product, *carboxypyridylglyceric acid,* $\mathrm{C_5H_3N}{<}\begin{matrix}\mathrm{COOH}\\ \mathrm{CH(OH).CH(OH)COOH}\end{matrix}$, which changes with ease to *acetonicotinic acid,* $\mathrm{C_5H_3N}{<}\begin{matrix}\mathrm{COOH}\\ \mathrm{COCH_3}\end{matrix}$ (compare B. **26,** 1501, and decomposition of β-naphthol and naphtho-quinone.)

The **anhydride** melts at 134° and the **imide** at 230° (A. **288,** 257).

On the esterification of quinolinic acid, see M. **29,** 227. The iodomethylate of the anhydride gives on treatment with Ag_2O and water **quinolinic acid methyl-**β**-betaïne,** $\overline{\mathrm{OCO[\beta](COOH)[\alpha]C_5H_3N}}\mathrm{(CH_3)}$; with benzene and $AlCl_3$ the anhydride yields β-benzoyl picolinic acid, $C_5H_3N[\beta]COC_6H_5[\alpha]COOH$ (M. **27,** 371; **32,** 747).

2,3-**Pyridin-dicarboxylic acid,** *Cinchomeronic acid,* m.p. 266° with decomposition, from cinchonine, cinchonidine, and quinine (compare C. 1900, II. 482), with nitric acid from *iso*quinoline with $KMnO_4$, etc.; by reduction with sodium amalgam it gives *cinchonic acid,* $C_7H_6O_5$, which decomposes on heating into CO_2 and *pyro-cinchonic acid* or dimethyl-maleïc acid anhydride (B. **18,** 2968). Cinchomeronic acid anhydride, m.p. 67°, yields with methyl alcohol the γ-methyl-ester acid, $C_5H_3N[\beta]CO_2H[\gamma]CO_2CH_3$, m.p. 173°, which on being transformed into γ-amino acid (compare B. **35,** 2841) and further transposition with

KOBr yields γ-amino-nicotinic acid. From the dimethyl ester, b.p.$_{28}$ 161°–171°, we obtain by a partial saponification β-methyl-ester acid, $C_5H_3N[\gamma]CO_2H[\beta]CO_2CH_3$. The γ-ester acid, on treating it with ICH_3 and silver oxide, gives the *methyl-ester* of *apophyllenic acid,* $\overline{O.CO[\beta]CO_2CH_3[\gamma]C_5H_3N}CH_3$ (compare Narcotine), whereas the β-ester acid gives the methyl ester of the isomeric methyl-γ-betaïne cinchomeronic acid (C. 1903, II. 888). With benzene and $AlCl_3$ the anhydride gives a mixture of γ-benzoyl-nicotinic acid and β-benzoyl-*iso*nicotinic acid (M. **30,** 355).

Cinchomeronimide, m.p. 230°, gives with alkali hypobromite β-amino-*iso*nicotinic acid, which, like anthranilic acid, tends to the formation of heterocyclic ortho condensation products (B. **35,** 2836); a reduction of the imide with tin and hydrochloric acid gives **cinchomeronimidine,** $C_5H_3N\left\{\begin{matrix}[\beta]CO\\ [\gamma]CH_2\end{matrix}\right. > NH$, m.p. 199°–200°.

Cinchomeryl-glycine ester, $C_5H_3N(CO)_2NCH_2CO_2R$, from potassium cinchomeronimide with chloracetic ester, is transposed like phthalyl-glycine ester by sodium ethylate into a derivative of the so-called *copyrine* (a twin nucleus of pyridine), **dioxy-copyrine-carboxylic ester,** $C_5H_3N\left\{\begin{matrix}[\beta]CO—NH\\ [\gamma]CO—CHCO_2R\end{matrix}\right.$. By splitting off the carboxyl group the latter has been converted into **dioxy-copyrine,** and by heating with HI and phosphorus into γ-ethyl-nicotinic acid (B. **35,** 1358, 2831; compare B. **37,** 2129).

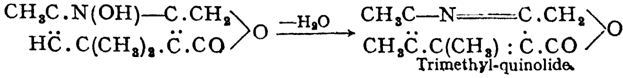
αγ-**Pyridinedicarboxylic acid, Lutidinic acid,** $C_5H_3N(CO_2H)_2 + 2H_2O$, m.p. 235° (A. **247,** 37). αβ′-**Pyridinedicarboxylic acid,** Iso*cinchomeronic acid,* crystallizes with 1 to 1½ H_2O, m.p. 236° (B. **19,** 1311). αα′-**Pyridinedicarboxylic acid, Dipicolinic acid,** m.p. 225° (A. **247,** 33). ββ′-**Pyridinedicarboxylic acid, Dinicotinic acid,** m.p. 314° (B. **19,** 286).

Homologous Pyridine-dicarboxylic Acids.—γ-**Methyl-quinolinic acid,** *lepidinic acid,* $C_5(CH_3)H_2N(CO_2H)_2$, m.p. 186° with decomposition, from γ-methyl-quinoline (Lepidine), or better from *Bz*-hydroxy-α-chloro-lepidine, by oxidation with $KMnO_4$. The first body produced is α-chloro-lepidinic acid, which is reduced to lepidinic acid by HI and phosphorus (B. **31,** 796).

α-**Methyl-pyridine**-α′γ-**dicarboxylic acid,** *Uvitonic acid,* $C_5(CH_3)H_2N(CO_2H)_2$, m.p. 244°, is formed by the action of alcoholic ammonia upon pyroracemic acid.

Lutidine-dicarboxylic acid, *αα′-dimethyl-ββ′-pyridine-dicarboxylic acid,* $C_5H(CH_3)_2N(CO_2H)_2$, m.p. 316°, from methenyl-bis-aceto-acetic ester with ammonia, or by oxidation with N_2O_3 from its dihydro-derivative obtained from methylene-bis-aceto acetic ester with ammonia (A. **241,** 31; **281,** 94); hydrazide and azide (see B. **33,** 1114).

Trimethyl-quinolinic acid, $C_5(CH_3)_3N[1,2](COOH)_2$, m.p. 195° with dec., is formed by the oxidation of the so-called trimethyl-quinolide, m.p. 152°, which results from the *pseudo*-oxime of keto-hexenyl-tetronic acid, the condensation product of tetronic acid with mesityl-oxide:



$$\left.\begin{matrix}CH_3C.N(OH)—C.CH_2\\ H\ddot{C}.C(CH_3)_2.\ddot{C}.CO\end{matrix}\right\rangle O \xrightarrow{-H_2O} \left.\begin{matrix}CH_3C—N{=\!=\!=}C.CH_2\\ CH_3\ddot{C}.C(CH_3):\dot{C}.CO\end{matrix}\right\rangle O.$$

Trimethyl-quinolide.

The trimethyl quinolinic acid, on further oxidation, yields **dimethyl pyridine-$\alpha\beta\beta'$-tricarboxylic acid** and **γ-methyl-pyridine-tetracarboxylic acid,** which by rejection of CO_2 yield various other carboxylic acids (A. **322,** 351).

($\alpha\alpha'\gamma$)-Trimethyl-pyridine-($\beta\beta'$)-dicarboxylic Acid, *Collidinedicarboxylic Acid,* $C_5(CH_3)_3N(CO_2H)_2$. The *diethyl ester* is prepared by the oxidation of dihydro-collidine dicarboxylic ester in alcoholic solution with nitrous acid. It is the foundation substance for the preparation of a series of higher and lower pyridine carboxylic acids.

C. *Pyridine Tricarboxylic Acids.*—**$\alpha\beta\gamma$-Pyridinetricarboxylic Acid,** *Carbo-cinchomeronic Acid,* $C_5H_2N(COOH)_3+1\frac{1}{2}H_2O$, melting at 250°, results upon oxidizing quinine, cinchonine, various decomposition products of these alkaloids, and γ-methyl quinolinic acid, etc., with potassium permanganate. Consult C. 1897, II. 308, for the esterification of this acid. **$\alpha\alpha'\gamma$-Pyridinetricarboxylic acid,** melting with decomposition at 145°, is obtained from symmetrical collidine or from uvitonic acid (A. **228,** 29). **$\alpha\beta'\gamma$-Pyridinetricarboxylic acid,** *Berberonic Acid,* obtained by the action of nitric acid upon the alkaloid berberine, melts at 235° (B. **25,** R. 582). **1,2,5-Pyridinetricarboxylic acid,** $(+2H_2O)$, decomposes at 130° (B. **19,** 1309).

D. *Pyridine Tetracarboxylic Acids.*—**$\alpha\alpha'\beta\gamma$-Pyridinetetracarboxylic Acid,** $C_5HN(COOH)_4(+2H_2O)$, melting at 227°, is obtained from collidine carboxylic acids or from *flavenol* (p. 195), a quinoline derivative (B. **17,** 2927). Consult B. **19,** 1309, for the *$\alpha\alpha'\beta\beta'$-acid,* etc.

E. **Pyridinepentacarboxylic Acid,** $C_5N(CO_2H)_5+2H_2O$, decomposing at 220°, is formed by the oxidation of collidine dicarboxylic acids.

II. *Oxypyridine Carboxylic Acids.*—The views expressed on p. 170 relative to the oxypyridines or pyridones apply to the constitution of the oxypyridine carboxylic acids. The latter are obtained with remarkable ease from the corresponding pyrone carboxylic acids by the action of ammonia. When heated they break down, as a rule, quite readily into carbon dioxide and pyridones.

A. *Monoxypyridine Carboxylic Acids.*—**α-Hydroxypyridine-β'-carboxylic Acid,** *Oxynicotinic Acid,* $C_5H_4ON(COOH)$, melting at 303°, is produced when ammonia acts upon coumalic acid ester, and by the elimination of carbon dioxide from hydroxyquinolinic acid.

n-Hydroxypyridine-β-carboxylic Acid, melting with decomposition at 255°, is made from 1-aminonicotinic acid (p. 175), and in various other ways (A. **288,** 265; M. **9,** 145). **γ-Hydroxypyridine-β-carboxylic Acid,** *Oxynicotinic Acid,* $(+H_2O)$, melting at 250°, is produced by the action of ammonia upon comanic acid. **α-Hydroxypyridine-$\alpha'\beta'$-dicarboxylic Acid,** *Oxyquinolinic Acid,* $C_5H_3ON(COOH)_2$, decomposing at 254°, is obtained from quinolinic acid by the potash fusion, or from its methyl ether, *methoxyquinolinic acid,* melting at 140°, which results when potassium permanganate acts upon amidocarbostyril ether. **α-Oxylepidinic acid,** $C_5H_2ON(CH_3)(COOH)_2$, from dioxylepidine (B. **31,** 802). **γ-Hydroxypyridine-$\alpha\alpha'$-dicarboxylic Acid,** *Ammonchelidonic Acid, Chelidamic Acid,* is obtained by the action of ammonia upon chelidonic acid.

$\alpha\gamma$-Dimethyl-α'-hydroxypyridine-β-carboxylic Acid, *Pseudo-lutidostyril Carboxylic Acid,* $C_5(CH_3)_2H_2ON(COOH)$, results upon heating HCl-β-aminocrotonic ester to 130° (B. **24,** R. 632). ***N*-Phenyllutidone carboxylic acid,** $C_5H(CH_3)_2(C_6H_5)ON(COOH)$, is similarly produced, together with γ-oxyquinaldine, upon heating β-anilinocrotonic ester. ***αα′*-Lutidone-*ββ′*-dicarboxylic Acid,** $C_5(CH_3)_2HON(COOH)_2$, melting at 267°, results when ammonia acts upon dimethyl pyrone dicarboxylic ester. Pentachloride of phosphorus converts it into ***γ*-chlorolutidine dicarboxylic acid,** melting at 224°, which yields ***γ*-aminolutidine dicarboxylic acid** with ammonia at 130° (B. **27,** 1323).

B. *Dioxypyridine Carboxylic Acids.*—**Dihydroxypicolinic Acid,** $C_5H_4O_2N(COOH)$, *Comenamic Acid,* is derived from comenic acid by heating with ammonia.

***α′γ*-Dihydroxypicoline-*β′*-carboxylic acid,** $C_5H_3(CH_3)O_2N(CO_2H)$, is obtained as an ester by sodium ethylate condensation of malonic ester (1 mol.) with β-aminocrotonic acid ester (1 mol.).

***αα′*-Dihydroxy-nicotinic acid,** m.p. 198°, from isaconitic acid ester, $(COOR)_2CH.CH:CHCO_2R$, with NH_3, with PCl_5 gives dichloronicotinic acid, m.p. 144° (J. pr. Ch. 2, **58,** 433).

1,5-Dihydroxy-dinicotinic acid, $C_5H_3O_2N(CO_2H)_2$, is obtained as ester and ether from dicyano-glutaconic acid ester, $CO_2RC(CN):CH.CH(CN)CO_2R$, and from ethoxy-coumalinic acid ester with NH_3. It yields **dichloro-dinicotinic acid ester,** m.p. 76° (B. **31,** 1241; **32,** 779; C. 1898, I. 1131; A. **297,** 87). ***αα′*-Dihydroxynicotinic acid,** *citrazinic acid,* by heating citramide, $CONH_2C(OH)(CH_2CONH_2)_2$, with H_2SO_4; for the conversion of citrazinic acid into dichloro- and di-iod*iso*nicotinic acid, see C. 1900, I. 818. *αα₁-Dichloro-*iso*nicotinic acid* with aniline forms $\alpha\alpha_1$-dianilino-*iso*nicotinic acid, and with potassium sulphydrate *dithio-*iso*nicotinic acid,* $C_5H_2N(SH)_2CO_2H$, m.p. 230° (B. **35,** 2933). With chloroform and alkali citrazinic acid has been made to yield a **dihydroxy-pyridine-aldehydo-carboxylic acid** (B. **29,** R. 1105).

***α*-Methyl-*α′β′*-dihydroxy-*iso*-nicotinic acid,** from chloracetone, oxaloacetic ester, and NH_3.

12. *Pyridyl-substituted acids of the fatty series* are known in but small numbers. ***αββ′*-Trichloropyridyl-*γ*-acetic acid,** $(C_5Cl_3HN)CH_2CO_2H$, m.p. 145°, by transformation of tetrachloropyridine with Na-malonic ester to **trichloropyridylmalonic ester,** m.p. 64°, and breaking up of the latter, gives methyltrichloropyridine on superheating (C. 1903, I. 1141). Some pyridyl lactic acids have been examined with regard to their connection with alkaloids. **Picolyl-*α*-lactic acid,** $[C_5(CH_3)H_3N]C(OH)(CH_3)COOH$, is obtained by saponification from its nitrile, the cyano-hydrin of picolyl methyl ketone (B. **28,** 1765).

***β*,1-Pyridyl-lactic Acid,** $C_5H_4N.CH_2CH(OH)COOH$, melting at 125°, is prepared by decomposing its *ortho-chloride,* chloral-picoline, $C_5H_4NCH_2CH(OH)CCl_3$, with soda, whereas with alcoholic potash the product is—

Pyridyl-*α*-acrylic acid, $C_5H_4N.CH:CH.COOH$. Bromine converts this acid into *pyridyldibromopropionic acid,* and hydrobromic acid changes it to *pyridylmonobromopropionic acid,* $C_5H_4.CHBr.CH_2.COOH$ (A. **265,** 221; C. 1902, I. 1232). ***α*,2-Picolyl acrylic acid,** $[C_5(CH_3)H_3N]CH(:CH_2)COOH$, is obtained from picolylbromopropionic acid, the reaction product of PBr_3 and picolyl-α-lactic acid.

α-, *β*-, and *γ*-**Pyridoylacetic ester,** $(C_5H_4N)COCH_2.CO_2C_2H_5$, are formed from the pyridine carboxylic esters with acetic ester and sodium ethylate; they show the well-known transformations of the *β*-ketonic acid esters (B. **34,** 4234).

HYDROPYRIDINE DERIVATIVES.

The reduction of the pyridines with zinc and HCl, or, better, with sodium and boiling alcohols, or by electrolysis (B. **29,** R. 1122; C. 1897, I. 388), produces hydropyridines, and especially the hydrated bodies called *piperidines.*

(*a*) *Dihydro-pyridine derivatives* are obtained in the pyridine syntheses from aldehydes with *β*-diketo-compounds and NH_3. Compare *Dihydro-collidine dicarboxylic ester, dihydro-lutidine dicarboxylic ester* (from formaldehyde, aceto-acetic ester, and NH_3), dihydrodiacetyl-lutidine, etc.; Dihydro-*β*,*β*₁-diacetylcollidine, $CH_3CH{<}\begin{matrix}C(COCH_3):C(CH_3)\\C(COCH_3):C(CH_3)\end{matrix}{>}NH$, m.p. 152°, is formed from ethylidene acetylacetone with amino-acetylacetone. By oxidation with N_2O_3 or dilute nitric acid these dihydro-derivatives are usually dehydrated with ease, pyridines being formed. The dihydro-lutidine dicarboxylic ester is partly dehydrated on merely treating with HCl. Lutidine dicarboxylic ester is thus formed, while another portion is hydrated to hexahydro-lutidine dicarboxylic ester (B. **35,** 1788). On boiling with alkalies the dihydro-pyridines are split up with formation of NH_3; some of the products undergo carbo-cyclic condensation. Dihydro-collidine dicarboxylic ester gives 3,5-dimethyl-Δ^2-*cyclo*-hexenone; concentrated alkalies disintegrate dihydro-collidine dicarboxylic ester to mono-carboxylic ester, and further to dihydro-collidine (B. **31,** 1025, 1033). Some dihydro-pyridines have been obtained as easily resinified liquids of penetrating odour from alkyl pyridinium iodides by treatment with potash (B. **14,** 1497). On the formation of trimethyl dihydro-pyridine from the oxime of methylheptenone with P_2O_5, see A. **319,** 77.

(*b*) *Tetrahydropyridines.*—*Piperideïnes* are formed, besides large quantities of piperidines, during the reduction of pyridine with sodium and alcohol. They can be isolated by means of their dibromides, from which they are easily regenerated by reduction with zinc dust and sulphuric acid. The bases so obtained are probably Δ^β-piperideïnes. They are reduced with great difficulty, and only by means of HI and phosphorus, to saturated piperidines. With acid chlorides and NaHO they yield *N*-acyl compounds in the usual way (B. **38,** 3042, 3928; **40,** 3199).

Quite a different behaviour is shown by the Δ^α-tetrahydropyridines (Lipp, A. **289,** 173; **294,** 135; *cf.* A. **304,** 54; B. **32,** 61):

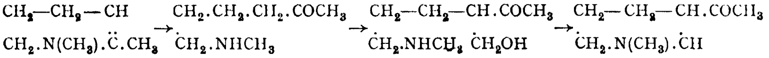
$$\begin{matrix}CH_2.CH_2Br\\ \dot{C}H_2.CH_2.COCH_3\end{matrix} \xrightarrow{NH_3} \begin{matrix}CH_2CH_2.NH\\ \dot{C}H_2.CH:\dot{C}CH_3\end{matrix}$$

They are obtained synthetically from the unstable *δ*-amino-ketones, or from *δ*-bromo-ketones with NH_3 or primary amines.

They are reduced to the corresponding piperidines by merely treating them with tin and HCl, and are easily split up to δ-amino-ketone derivatives—*e.g.*, with benzoyl chloride and NaHO. This splitting occurs with special ease in the *N*-alkylated and *N*-arylated Δ^α^-piperideïnes, so that, *e.g.*, *N*-phenyl-Δ^{α}-pipecoleïne is only stable in the form of its salts. The Δ^{β}- and Δ^{α}-piperideïnes therefore correspond to the 2,5- and 3,4-dihydro-pyrrols respectively.

β-Ethylpiperideïne, b.p. 158°, **β-Ethyl-γ-methylpiperideïne,** b.p. 177°, and **α-Methyl-β_1-ethylpiperideïne,** from the corresponding pyridines with Na and alcohol.

Δ^{α}-Tetrahydropicoline, *Pipecoleïne*, $C_6H_{11}N$, b.p. 132°, is reduced by tin and HCl to pipecoline, and is split up by benzoyl chloride and NaHO to δ-benzoylamino-butyl methyl ketone, and by nitrous acid to γ-acetobutyl alcohol (A. **289,** 173; B. **42,** 1242). **α-Phenyl-Δ^{α}-piperideïne,** m.p. ca. 18°, b.p. 276°, from δ-amino-valerophenone (B. **41,** 2010). **α,β-Dimethyl-Δ^{α}-piperideïne,** b.p. 155°, ***N*-Methyl-Δ^{α}-pipecoleïne,** b.p. 146°, gives, with benzoyl-chloride and NaHO, the benzoyl compound, and with hydroxylamine and semicarbazide the oxime and semicarbazone respectively of δ-methyl-amino-butyl methyl ketone. This easy break-up also explains the remarkable action of formaldehyde upon *N*-methyl-pipecoleïne, leading to *N*-methyl-β-acetylpiperidine, which may be interpreted as follows:

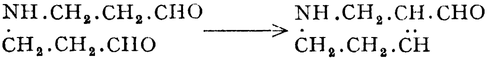


$$\begin{array}{l}CH_2—CH_2—CH\\ CH_2.N(CH_3).\ddot{C}.CH_3\end{array}\rightarrow\begin{array}{l}CH_2.CH_2.CH_2.COCH_3\\ \dot{C}H_2.NHCH_3\end{array}\rightarrow\begin{array}{l}CH_2—CH_2—CH.COCH_3\\ \dot{C}H_2.NHCH_3\ \dot{C}H_2OH\end{array}\rightarrow\begin{array}{l}CH_2—CH_2—CH.COCH_3\\ \dot{C}H_2.N(CH_3).\dot{C}H\end{array}$$

α-*N*-Propyl-Δ^{α}-piperideïne is known as **γ-Coniceïne**. On **Piperideïne** from piperidine oxide, see B. **25,** 2782. An isomeric tetrahydro-pyridine is obtained from piperidine sulphonic acid by fusion with potash (B. **34,** 2761). On a tetrahydro-pyridine from methyl heptenyl-amine, see B. **38,** 2803.

Keto-derivatives of di- and tetrahydro-pyridines are represented by the *N*-alkyl derivatives of the pyridones and dioxy-pyridines or glutaconimides (see above).

β-Aldehydes of Δ^{β}-piperideïne are obtained in the hydrolysis of imino-dipropionic acetal (Vol. I.) and its *N*-alkyl substitution products by the intramolecular condensation of the primary imino-dipropionic aldehyde (B. **38,** 4154; **40,** 4679):



$$\begin{array}{l}NH.CH_2.CH_2.CHO\\ \dot{C}H_2.CH_2.CHO\end{array}\longrightarrow\begin{array}{l}NH.CH_2.CH.CHO\\ \dot{C}H_2.CH_2.\ddot{C}H\end{array}$$

Δ^{β}-Piperideïne-β-aldehyde only exists in a polymolecular amorphous form. Its *hydrochloride* melts at 145° with dec., its N-*benzoyl compound* at 91°. Its *oxime*, m.p. 145°, on being dehydrated with $SOCl_2$, yields **Δ^{β}-piperideïne-β-nitrile,** b.p.$_{0\cdot 2}$ 48°, from which racemic cincholoiponic acid is obtained by the addition of sodium malonic ester and saponification.

***N*-Methyl-Δ^{β}-piperideïne-β-aldehyde,** b.p.$_{0\cdot 17}$ 40°–43°, has an odour resembling amine.

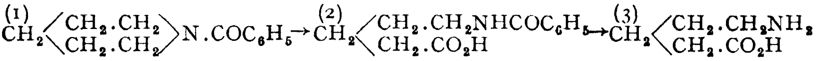
The **methyl-Δ^{β}-piperideïne-β-nitrile,** obtained by way of the oxime, yields on saponification the alkaloid arecaidin. ***N*-Ethyl-Δ^{β}-piperideïne-β-aldehyde,** b.p.$_{0\cdot 06}$ 53°.

(*c*) *Hexahydropyridines, Piperidines.*—**Hexahydropyridine, Piperidine,** *Pentamethylene imine*, $CH_2<\begin{smallmatrix}CH_2—CH_2\\CH_2—CH_2\end{smallmatrix}>NH$, boiling at 106·2° (A. **345,** 277), is a liquid dissolving quite readily in water and in alcohol. Its odour is like that of pepper. It occurs attached to piperic acid (p. 285) as piperine in pepper, and is produced when piperine is heated together with alcoholic potash. It may be synthesized (1) by heating pentamethylenediamine hydrochloride; (2) by heating ε-chlor- and ε-bromamylamine with caustic potash (previously mentioned); and (3) by the reduction of pyridine, into which it passes when heated with sulphuric acid to 300°, or, better, with nitrobenzene to 260°, or by boiling with silver oxide or silver acetate in glacial acetic acid (B. **25,** 1620).

Decomposition of Piperidine.—The piperidine ring is ruptured in the following reactions:

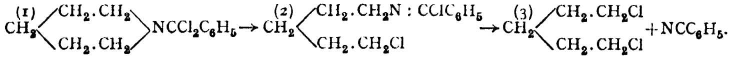
1. When piperidine is heated to 300° with hydriodic acid it is converted into ammonia and *n*-pentane.

2. The oxidation of benzoylpiperidine (1) with potassium permanganate produces **δ-benzoylamino-*n*-valerianic acid** (2), which, with caustic potash, produces δ-amino-*n*-valerianic acid (3) or homopiperidinic acid (B. **17,** 2544); but piperidyl urethane, oxidized with nitric acid, yields carboxethyl-aminobutyric acid, which, with caustic potash, gives γ-amino-butyric acid or piperidinic acid:



$$\overset{(1)}{CH_2}<\begin{smallmatrix}CH_2.CH_2\\CH_2.CH_2\end{smallmatrix}>N.COC_6H_5 \rightarrow \overset{(2)}{CH_2}<\begin{smallmatrix}CH_2.CH_2NHCOC_6H_5\\CH_2.CO_2H\end{smallmatrix} \rightarrow \overset{(3)}{CH_2}<\begin{smallmatrix}CH_2.CH_2NH_2\\CH_2.CO_2H\end{smallmatrix}$$

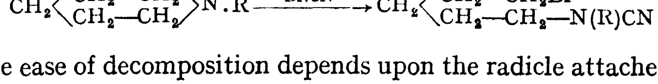
3. On heating benzoylpiperidine with PCl_5, the benzoyl-piperide chloride (1) first formed is split up to ε-chloramyl-benzimide chloride (2), which, on distillation, breaks up into αε-dichloro-pentane (3) and benzo-nitrile (v. Braun, B. **37,** 2915, 3210; **44,** 1039):



$$\overset{(1)}{CH_2}<\begin{smallmatrix}CH_2.CH_2\\CH_2.CH_2\end{smallmatrix}>NCCl_2C_6H_5 \rightarrow \overset{(2)}{CH_2}<\begin{smallmatrix}CH_2.CH_2N:CClC_6H_5\\CH_2.CH_2Cl\end{smallmatrix} \rightarrow \overset{(3)}{CH_2}<\begin{smallmatrix}CH_2.CH_2Cl\\CH_2.CH_2Cl\end{smallmatrix} + NCC_6H_5.$$

Compare the analogous action of PCl_5 upon dimethyl benzamide.

4. The *N*-alkyl and *N*-amylpiperidines are split up by cyanogen bromide to ε-bromamyl-cyanalkylamines (B. **40,** 3914):

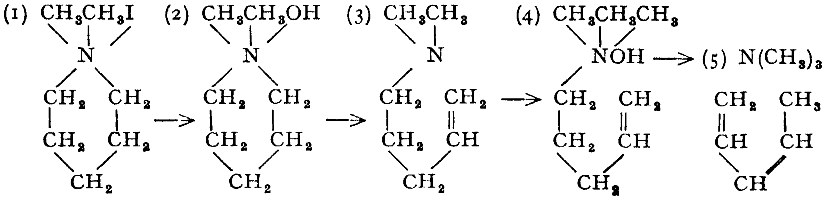


$$CH_2<\begin{smallmatrix}CH_2—CH_2\\CH_2—CH_2\end{smallmatrix}>N.R \xrightarrow{Br.CN} CH_2<\begin{smallmatrix}CH_2—CH_2Br\\CH_2—CH_2—N(R)CN\end{smallmatrix}$$

The ease of decomposition depends upon the radicle attached to the nitrogen.

5. Piperidine and methyl iodide form dimethylpiperidinium iodide (1), which moist silver oxide converts into dimethylpiperidinium hydroxide (2). This breaks down, on distillation, into dimethylpiperidine, the Δ^δ-pentenyldimethylamine (3) and water. If Δ^δ-pentenyldimethylamine be converted into Δ^δ-pentenyltrimethylammonium hydroxide (4), and the latter be distilled, it will break down into piperylene or $\Delta^{\alpha\gamma}$-pentadiene (5), trimethylamine, and water (A. W. Hofmann, Ladenburg, B. **16,** 2058, and **42,** 2532; compare the decomposition of

the pyrrolidines). The diagram affords a review of the preceding decomposition reactions:



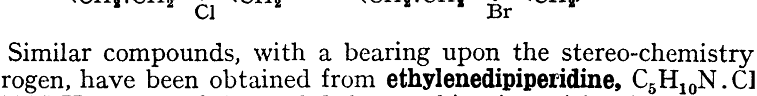
Piperidine Derivatives.—As an imide base, piperidine is capable of forming a nitroso-compound, N-alkyl, and N-acyl derivatives. On the physiological action of piperidine derivatives, see B. **34,** 2408.

Nitroso-piperidine, $C_5H_{10}N.NO$, b.p. 218°, from piperidine with nitrous acid, is converted by reduction into **piperyl-hydrazine,** $C_5H_{10}N.NH_2$, b.p. 146°, which, on oxidation, yields dipiperidyl tetrazone $(C_5H_{10}N)_2N_2$, m.p. 45° (compare C. 1905, I. 1260). On the decomposition of nitroso-piperidine and its homologues by electrolysis, see B. **31,** 2272, 2276.

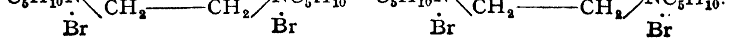
N-**Methylpiperidine,** $C_5H_{10}NCH_3$, b.p. 107°; *N*-**Ethyl-,** *N*-**Propyl-,** *N*-*iso***Amylpiperidine,** b.p. 128°, 149°, and 187°; *N*-**Benzylpiperidine,** b.p. 245° (B. **32,** 2507); *N*-**Allylpiperidine,** b.p. 152° (C. 1899, I. 1066). *N*-**Phenylpiperidine,** b.p. 258°, from $a\epsilon$-dibromo-pentane and aniline, is, curiously enough, also obtained by heating piperidine with bromo- and iodo-benzene (compare B. **21,** 1921; **23,** 1388); *N*,a- and *N*,β-**naphthyl-piperidine,** b.p.$_{35}$ 215° and m.p. 58° respectively, from the naphthols with piperidine (B. **29,** 1175).

By oxidation with H_2O_2 piperidine is converted into its *oxide*, C_5H_{10}: NH: O or C_5H_{10}: N.OH, m.p. 39°, b.p.$_{55}$ 110°; this, with phenyl *iso*cyanate, gives an o-*carbanilido derivative,* C_5H_{10}: $N.OCONHC_6H_5$, but on alkylation it gives *N*-alkyl-piperidine oxides, which are also obtained direct from the *N*-alkyl-piperidines with H_2O_2, and correspond to the dialkyl aniline oxides: *N*-**Methyl-piperidine oxide,** C_5H_{10}: $N(CH_3)$: O, *N*-**propyl-piperidine oxide,** m.p. 105°, *N*-**benzyl-piperidine oxide,** m.p. 148°. On heating with acids they easily give up their oxygen and regenerate the piperidines; on heating alone the *N*-alkyl-piperidine oxides break up into piperidine oxide and olefines (B. **37,** 3228).

On heating *N*(β-chlorethyl)piperidine, *N*(γ-bromopropyl)piperidine, etc., the isomeric dicyclic ammonium salts are obtained (B. **32,** 850; **34,** 357; **39,** 2875, 4347; **40,** 424; **42,** 545):



Similar compounds, with a bearing upon the stereo-chemistry nitrogen, have been obtained from **ethylenedipiperidine,** $C_5H_{10}N.C$ $CH_2NC_5H_{10}$, m.p. 4°, b.p. 263°, by combination with alkylene dib mides (B. **32,** 988; **35,** 3047; C. 1904, I. 673):



Ethylene dipiperidine with trimethylene bromide, and trimethylene dipiperidine with ethylene bromide, give stereo-isomeric inactive compounds (compare B. **44,** 480).

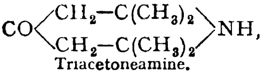
N-**Piperidyl-acetaldehyde,** $C_5H_{10}N.CH_2CHO$, m.p. 103° (B. **34,** 2541). *N*-**Piperidylacetone,** $C_5H_{10}N.CH_2COCH_3$ (C. 1900, II. 582). *N*-**Piperidylacetic acid,** $C_5H_{10}N.CH_2CO_2H + H_2O$, and homologues (B. **31,** 2839; **32,** 722).

N-**Acetylpiperidine,** $C_5H_{10}NCOCH_3$, boils at 226°. *N*-**Benzoylpiperidine,** $C_5H_{10}NCOC_6H_5$, melting at 48°, condenses when heated with benzaldehyde to dibenzyl-pyridine. **Piperidylurethane,** $C_5H_{10}NCO_2C_2H_5$, boils at 211° (compare also C. 1898, I. 257). The oxidation of benzoylpiperidine and piperylurethane leads to the rupture of the piperidine nucleus. **Piperine,** the alkaloid, is the piperide of piperic acid.

The *homologous piperidines* result when the homologous pyridines are reduced with sodium and alcohol. They are called **pipecolines,** $C_5H_9(CH_3)NH$, **lupetidines,** $C_5H_8(CH_3)_2NH$, **copellidines,** $C_5H_8(CH_3)(C_2H_5)NH$, etc. (compare B. **28,** 2270).

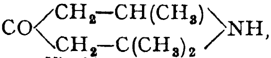
The alkyl piperidines contain asymmetric carbon atoms, hence different members of this class of bases have been decomposed, by means of their bitartrates, into optically active components—*e.g.*, α-**pipecoline** (B. **29,** 43, 422), the **copellidine,** boiling at 163° (B. **29,** 1959), obtained from aldehyde collidine, and β-**propylpiperidine,** boiling at 174° (B. **30,** 1060), isomeric with coniïne, which has been synthetically prepared from ϵ-chloro-β-propyl-amylamine; α-**ethylpiperidine,** b.p. 143° (B. **33,** 3483, 3513), and β-**ethylpiperidine,** b.p. 155° (B. **31,** 2141). The great increase of optical activity on introducing alkyl groups at the N-atom of the β-alkylpiperidines is remarkable (B. **32,** 2520; **34,** 2420). $\alpha\alpha_1$-**Dimethylpiperidine,** *Lupetidine,* is obtained in a fissile racemic form, boiling at 133°, and in a meso-form, b.p. 128° (B. **32,** 2520; **34,** 2426). The same applies to $\alpha\alpha_1$-**diphenylpiperidine,** which is liquid in its racemic form, and melts at 71° in the meso-form, while the $\alpha\alpha_1$-**phenylmethyl piperidine** occurs in two stereo-isomeric, optically fissile modifications (B. **33,** 2842; **34,** 1616). $\alpha\alpha_1$-**Tetramethylpiperidine,** b.p. 156° (see C. 1905, II. 1185).

Keto-derivatives of the Piperidine Series.—The δ-lactams (Vol. I.) are α-keto-piperidines or α-piperidones. Among the γ-keto-piperidines are the following:



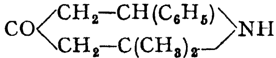
$CO\left\langle\begin{matrix}CH_2-C(CH_3)_2\\CH_2-C(CH_3)_2\end{matrix}\right\rangle NH,$

Triacetoneamine.



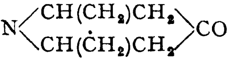
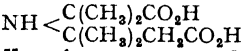
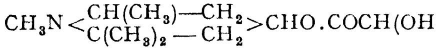
$CO\left\langle\begin{matrix}CH_2-CH(CH_3)\\CH_2-C(CH_3)_2\end{matrix}\right\rangle NH,$

Vinyldiacetoneamine.



$CO\left\langle\begin{matrix}CH_2-CH(C_6H_5)\\CH_2-C(CH_3)_2\end{matrix}\right\rangle NH,$

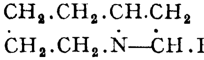
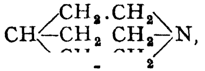
Benzaldiacetoneamine.

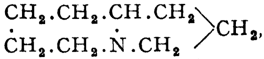
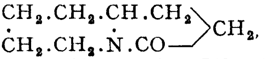
which result from phorone with NH_3 and from diacetoneamine with acetaldehyde or benzaldehyde (compare B. **32,** *2244*). Triacetoneamine, $\alpha\alpha_1$-**tetramethyl-γ-ketopiperidine,** is of special interest on account of its structural similarity with tropine and tropinone,  $CH_8N\left\langle\begin{matrix}CH(CH_2)CH_2\\CH(\dot{C}H_2)CH_2\end{matrix}\right\rangle CO$ (see Atropine); as the latter gives tropinic acid, so triacetone-amine on oxidation gives the acid  $NH<\begin{matrix}C(CH_3)_2CO_2H\\C(CH_3)_2CH_2CO_2H\end{matrix}$ (A. **198,** 74). On reduction it gives **triacetone-alkamine,** *tetramethyl-hydroxy-piperidine,* $C_5H_6(CH_3)_4(OH)N$, which splits off water and passes into a piperideïne called *triacetonine*. With bromine triacetone-amine yields **dibromotriacetone-amine,** which is converted by ammonia into **tetramethylpyrroline-carboxylic acid amide** (see p. 38). With mercaptans, triacetone-amine expels water and yields **triacetonine-γ-alkyl-sulphides**—*e.g.*, $C_5H_6(CH_3)_4(SC_2H_5)N$. On the other hand, vinyl-diacetone-amine, $\alpha\alpha_1$-trimethyl-γ-ketopiperidine, with mercaptans yields normal mercaptoles which can be oxidized to sulphonals (B. **31**, 3145). By the reduction of vinyl-diacetone-amine oximes, m.p. 151°, two stereo-isomeric **γ-aminotrimethylpiperidines,** $C_5H_7(CH_3)_3(NH_2)N$ (α-, m.p. 26°, b.p.$_{22}$ 85°; β-oil, b.p.$_{22}$ 83°) are formed, which, on treatment with nitrous acid, yield two stereo-isomeric **vinyl-diacetone-alkamines, γ-hydroxytrimethylpiperidines,** $C_5H_7(CH_3)_3(OH)N$, m.p. 137° and 161°, the latter of which is transposed by sodium amylate into the former. The mandelic acid esters of the corresponding *N*-**methyl-vinyl-diacetone-alkamines,**  $CH_3N{<}\begin{matrix}CH(CH_3)-CH_2\\C(CH_3)_2-CH_2\end{matrix}{>}CHO.COCH(OH)C_6H_5$, are of interest, inasmuch as the ester in the stable isomeride (oil) is physiologically ineffective, whereas the ester from the unstable isomeride, melting at 113°, is used as a mydriatic under the name of *euphthalmine*.

C-**Piperidine-sulphonic acid,** $(C_5H_{10}N)SO_3H$, m.p. 188°, from piperidine and amido-sulphonic acid at 180° (B. **34**, 2757).

The reduction of pyridine-alkines with Na and alcohol produces piperidine-alkines. From methyl-α-picoline (*picolyl-alkine*), we obtain **α-pipecolyl-alkine,** $(C_5H_{10}N)[\alpha]CH_2CH_2OH$, m.p. 39°, b.p. 234°, which on reduction with CrO_3 gives **piperidyl-α-acetic acid,** $(C_5H_{10}N)[\alpha]CH_2CO_2H$, m.p. 214° (B. **36**, 2905). *N*-**Methyl-pipecolyl-alkine,** on heating with HCl, gives *N*-**methyl-α-vinyl-piperidine,** b.p.$_{12}$ 60° (B. **34**, 1889).

α-Pipecolyl-methyl-alkine, $(C_5H_{10}N)[\alpha]CH_2CH(OH)CH_3$, m.p. 57°, b.p. 226° to 229°, on being deprived of water by means of P_2O_5, yields two stereo-isomeric α-propenyl-piperidines, $(C_5H_{10}N)[\alpha]CH:CHCH_3$, m.p. 18°, b.p. 169°, and m.p. 15°, b.p. 167°, which have been split up into optically active components by means of the bitartrates (B. **42**, 107). **α-Pipecolyl-ethyl-alkine,** $C_5H_{10}N[\alpha]CH_2CH(OH)C_2H_5$, m.p. 55°, b.p. 127°.

The iodides obtained from α-pipecolyl-alkines by means of HI are converted by treatment with alkali and intramolecular alkylation into the bi-cyclic tertiary bases,  $\begin{matrix}CH_2.CH_2.CH.CH_2\\ \cdot \qquad \cdot \qquad \cdot\\ CH_2.CH_2.N-CH.R\end{matrix}$, the so-called *conidines* (B. **40**, 1310; **43**, 2048). In a similar manner the iodide obtained from **γ-pipecolyl-alkine,** $(C_5H_{10}N)[\gamma]CH_2CH_2OH$, b.p. 228°, yields the bi-cyclic **quinuclidine,**  $CH\begin{matrix}CH_2.CH_2\\CH_2\;CH_2\\CH_2.CH_2\end{matrix}N$, b.p. 140°, which is of special interest on account of its structural similarity with the quinia-alkaloids (B. **42**, 124). **β-Ethyl-quinuclidine,** b.p. 191°, is similarly obtained from **ωγ-hydroxy-βγ-diethyl-piperidine,** $(C_5H_9N)[\beta]C_2H_5[\gamma]CH_2CH_2OH$, and has been obtained also in an active form (B. **38**, 3049). **α-Ethyl-piperyl-alkine,** $(C_5H_{10}N)[\alpha]CH(OH)C_2H_5$, m.p. 99°, is the inactive form of conhydrine. It is formed by the reduction of α-pyridyl ethyl ketones with Na and amyl-alcohol, and passes on further reduction into (*d* + *l*)-coniine.

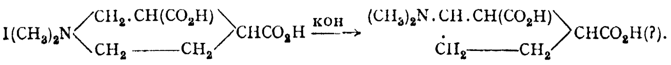
ω-Hydroxy-α-propylpiperidine, $(C_5H_{10}N)[\alpha]CH_2CH_2.CH_2OH$, b.p. 248°, is formed by the reduction of α-pyridyl-acrylic acid ester with Na and alcohol. On splitting off water by means of concentrated SO_4H_2 or P_2O_5 it yields a little **α-allylpiperidine,** $(C_5H_{10}N)[\alpha]CH_2CH:CH_2$, b.p. 171°, together with the bi-cyclic **piperolidine,**  $\left.\begin{array}{l}CH_2.CH_2.CH.CH_2\\ CH_2.CH_2.N.CH_2\end{array}\right\rangle CH_2$, b.p. 161°, which is also formed by reduction of **piperolidone,**  $\left.\begin{array}{l}CH_2.CH_2.CH.CH_2\\ CH_2.CH_2.N.CO\end{array}\right\rangle CH_2$, b.p. 126°, the lactam of **α-piperidyl-propionic acid,** $(C_5H_{10}N)[\alpha]CH_2.CH_2.CO_2H$, m.p. 148°, which is obtained by the reduction of α-pyridyl-acrylic acid (B. **42,** 94, 3420).

Piperidine-β-aldehydes have been obtained from piperideïne aldehydes by conversion into the γ-chloropiperidine aldehyde acetals by means of alcohol and HCl, and subsequent treatment with Na and alcohol. **Piperidine-β-aldehyde,** $(C_5H_{10}N.CHO)_2$, is only known in the bimolecular form. Its diethyl acetal boils at 55° (0·15 mm.) (B. **40,** 4695). *N*-**Ethylpiperidine-β-aldehyde,** b.p.$_{0\cdot 2}$ 44°, is also easily polymerized (B. **38,** 4170).

Sodium and alcohols reduce the pyridine carboxylic acids to *piperidine carboxylic acids.*

Pipecolinic Acid, $C_5H_{10}N(COOH)$, melting at 261°, is resolved by the bitartrate into *d*- and *l*-pipecolinic acids, melting at 270° (B. **29,** 2887). **Hexahydroquinolinic Acid,** $C_5H_9N(COOH)$, has been obtained, similar to the hydrophthalic acids, in two stereo-isomeric forms, melting at 227° and 253°, of which each in the form of its *nitroso*-compound can be decomposed into two optically active forms (consult B. **29,** 2665). **Hexahydrocinchomeronic acid** melts with decomposition at 256° (B. **29,** 2187).

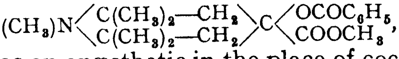
The iodomethylate of *N*-methyl-hexahydro-cinchomeronic acid is split up by alkali in a manner somewhat different from *N*-methylpiperidine iodo-methylate, as it forms a dimethylamino-*cyclo*-pentane dicarboxylic acid (M. **23,** 269):



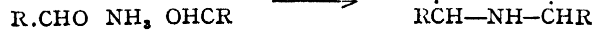
$$I(CH_3)_2N\left\langle\begin{array}{l}CH_2.CH(CO_2H)\\ CH_2 \text{———} CH_2\end{array}\right\rangle CHCO_2H \xrightarrow{KOH} \left.\begin{array}{l}(CH_3)_2N.CH.CH(CO_2H)\\ CH_2 \text{———} CH_2\end{array}\right\rangle CHCO_2H(?).$$

Quite similar behaviour is shown by the homologous cincholoiponic acid, a disintegration product of cinchonine (*q.v.*).

αα$_1$-Piperidinedicarboxylic acid, from dibromopimelic acid with NH_3 (see B. **34,** 2543).

An hydroxy-carboxylic derivative of the piperidine series is *Eucaïne,* a **tetramethyl-*N*-methyl-γ-benzoxy-piperidine-γ-carboxylic ester,**  $(CH_3)N\left\langle\begin{array}{l}C(CH_3)_2\text{—}CH_2\\ C(CH_3)_2\text{—}CH_2\end{array}\right\rangle C\left\langle\begin{array}{l}OCOC_6H_5\\ COOCH_3\end{array}\right.$, which has been recommended as an anæsthetic in the place of cocaïne (C. 1896, II. 709).

Many γ-piperidine-ββ$_1$-dicarboxylic esters have been obtained by condensation of acetone dicarboxylic esters with aldehydes and NH_3 or primary amines (J. pr. Ch. 2, **85,** 1):



$$\begin{array}{c}CO_2R.CH_2\text{—}CO\text{—}CH_2.CO_2R\\ R.CHO\quad NH_3\quad OHCR\end{array} \longrightarrow \begin{array}{c}CO_2R.CH\text{—}CO\text{—}CH.CO_2R\\ RCH\text{—}NH\text{—}CHR\end{array}$$

Coniine, or α-propylpiperidine, *tropine*, and *ecgonine* are other important piperidine compounds. They are alkaloids or decomposition products of the latter. They will be discussed later, in the chapter relating to alkaloids.

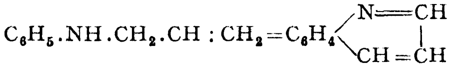
Condensed nuclei, obtained from pyridine, have been prepared in great numbers, and are arranged in the following groups: II. *Quinolines.* III. *Condensed Quinolines—e.g.*, naphthoquinolines, anthraquinolines, phenanthrolines, quinoquinolines. IV. iso*Quinolines.* V. *Phenanthridines.* VI. *Naphthyridines* and *Naphthinolines.* VII. *Acridines* (carbazacridines, quinacridines). VIII. *Anthrapyridines.* The vegetable alkaloids attach themselves as a distinct chapter to the preceding bodies.

II. QUINOLINE GROUP.

The quinoline bases, or benzopyridine group, occur with those of pyridine in bone-oil (coal-tar), and are obtained by distilling different alkaloids with lime. The parent substance of the group was first obtained by Gerhardt (1842) from the alkaloids quinine and cinchonine.

As regards synthetic methods, reactions, and isomerides, quinoline is a naphthalene in which an α-CH-group is replaced by N.

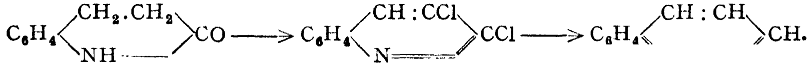
This was first shown by synthesizing quinoline from allylaniline. This is perfectly analogous to the synthesis of naphthalene from phenyl butylene (Königs):



$$C_6H_5.NH.CH_2.CH:CH_2 = C_6H_4\left\langle\begin{matrix}N=\!=CH\\ \quad| \\ CH=CH\end{matrix}\right.$$

Allyl Aniline. Quinoline.

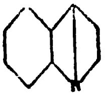
A more direct proof of the constitution of quinoline was effected through its formation from hydrocarbostyril; PCl_5 converts the latter into a dichloride, which upon heating with hydriodic acid yields quinoline (A. Baeyer, B. **12**, 1320):



$$C_6H_4\left\langle\begin{matrix}CH_2.CH_2\\NH\text{——}\end{matrix}\right\rangle CO \longrightarrow C_6H_4\left\langle\begin{matrix}CH:CCl\\N=\!=\!=\end{matrix}\right\rangle CCl \longrightarrow C_6H_4\left\langle\begin{matrix}CH:CH\\ \;\end{matrix}\right\rangle CH.$$

Hydrocarbostyril. αβ-Dichlor-quinoline. Quinoline.

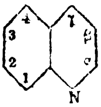
A " diagonal formula " has been suggested for quinoline because of its production in the distillation of acridine:



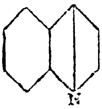
Owing to the intimate genetic relations prevailing between the quinoline and pyridine derivatives we must assume for the pyridine nucleus of quinoline the same linkages as in pyridine itself. Furthermore, later researches upon the formation of quinoquinolines from quinolines afford additional proof against the " diagonal formula " (A. **273**, 1).

Isomerisms of the Quinoline Derivatives:

We represent the three replaceable hydrogen atoms of the pyridine nucleus in quinoline by *α*, *β*, and *γ*; those of the benzene nucleus with 1, 2, 3, and 4:



II.



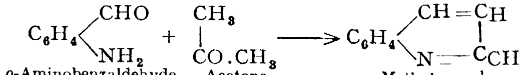
The positions 1, 2, 3, referred to the N-atom, correspond to the ortho-, meta-, and para-positions of the benzene derivatives; 4 is known as the *Ana*-position. These positions are designated as the affinities of the benzene nucleus with *o*-, *m*-, *p*-, and *a*. Another nomenclature designates the affinities of the pyridine nucleus as Py-1, -2, and -3; those of the benzene nucleus as B-1, -2, -3, and -4. Consequently, seven mono-derivatives of quinoline are possible (B. **19,** R. 443).

Syntheses of the Quinoline Derivatives:

1. The condensation of the ortho-amino-compounds of such benzene derivatives as have an oxygen atom attached to the third carbon atom of the side-chain.

In this way we obtain quinoline from *o-amino-cinnamic aldehyde*, $C_6H_4<^{NH_2}_{CH:CH.COH}$, *α*-methyl-quinoline from *o-amino-styryl methyl ketone*, and *α*-hydroxy-quinoline (carbostyril) from *o*-amino-cinnamic acid.

2. The condensation of *o*-aminobenzaldehyde or *o*-aminobenzoketones with substances containing the group —CH_2—CO— (*e.g.*, aldehydes, ketones, acetoacetic ester, malonic ester) to quinolines by means of sodium hydroxide is dependent upon the intermediate formation of such *o*-amino-derivatives (Friedländer, B. **16,** 1833; **25,** 1752):

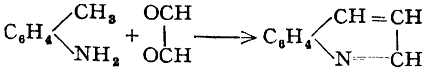


$$C_6H_4\begin{array}{l}\diagup CHO\\ \diagdown NH_2\end{array} + \begin{array}{c}CH_3\\ |\\ CO.CH_3\end{array} \longrightarrow C_6H_4\begin{array}{l}\diagup CH=CH\\ \qquad\qquad\ |\\ \diagdown N=CCH_3\end{array}$$

o-Aminobenzaldehyde. Acetone. *α*-Methylquinoline.

γ-Hydroxyquinolines are similarly formed from anthranilic acid with aldehydes, ketones, etc. (Ch. Zt. **17,** Rep. 258; see also B. **28,** 2809), and cinchoninic acid from isatinic acid with aldehydes (J. pr. Ch. [2], **66,** 263). Also hydroxyquinolines from *o*-acyl-amino-acetophenone (B. **32,** 3228; C. 1900, I. 426).

The synthesis of quinoline from *o*-toluidine and glyoxal and that of *β*-hydroxyquinaldine from *o*-toluidine and pyroracemic ester are similar (B. **27,** 628; **28,** R. 743):



$$C_6H_4\begin{array}{l}\diagup CH_3\\ \diagdown NH_2\end{array} + \begin{array}{c}OCH\\ |\\ OCH\end{array} \longrightarrow C_6H_4\begin{array}{l}\diagup CH=CH\\ \qquad\qquad |\\ \diagdown N=CH\end{array}$$

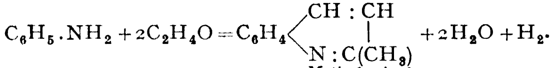
3. The production of quinoline and its derivatives substituted in the benzene nucleus by heating anilines with glycerol and sulphuric acid to about 140°, with the addition of nitrobenzene, or, better, arsenic acid (B. **29,** 703), as the oxidizing agent. This method is of universal application, and can be very readily executed (Skraup):

$$\underset{\text{Aniline.}}{C_6H_5.NH_2} + \underset{\text{Glycerol.}}{C_3H_8O_3} = \underset{\text{Quinoline.}}{C_9H_7N} + 3H_2O + H_2.$$

It is very probable that acroleïn first results, this then combines with the aniline derivative yielding acroleïn-aniline, which is oxidized to the quinoline derivative by the elimination of two hydrogen atoms by sulphuric acid. The halogen, nitro-, hydroxyanilines, toluidines, etc., behave similarly. The naphthylamines yield the naphthoquinolines; and the diamidobenzenes, the phenanthrolines.

Instead of using a mixture of the aromatic aniline and nitrobenzene, the corresponding nitro-body alone can be employed, which then is reduced in part by the hydrogen arising in the reaction. The first synthesis of this description was the preparation of alizarin blue from nitroalizarin, glycerol, and sulphuric acid (A. **201,** 333). The following may be regarded as further generalizations of these syntheses:

4. (*a*) Quinolines substituted both in the benzene and pyridine nucleus can be produced in the condensation of anilines with aldehydes, aided by sulphuric or hydrochloric acid (*Quinaldine syntheses* of Doebner and v. Miller). Aniline and acetaldehyde yield α-methylquinoline or quinaldine:

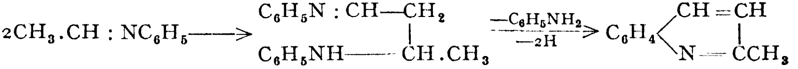


$$C_6H_5.NH_2 + 2C_2H_4O = C_6H_4\left\langle\begin{array}{l}CH:CH\\ \quad\ |\\ N:C(CH_3)\end{array}\right. + 2H_2O + H_2.$$

α-Methylquinoline.

All aldehydes of the formula $CHO.CH_2R$ react like acetaldehyde. The first step in the reaction consists in two molecules combining to unsaturated aldehydes, $CHO.CR:CH.CH_2R$, or condensing to aldols corresponding to them. These then act upon the anilines and form quinoline bases with a CH_2-group in the α-position.

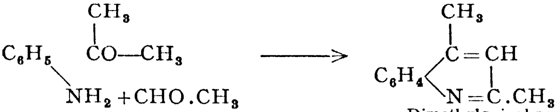
It is very probable that alkylidene anilines formed at first change to dimolecular, aldol-like condensation products, which split off aniline and become quinaldines (B. **25,** 2864; **29,** 59; compare formation 2 of the indols):



$$2CH_3.CH:NC_6H_5 \longrightarrow \begin{array}{l}C_6H_5N:CH—CH_2\\ \qquad\qquad\quad |\\ C_6H_5NH——CH.CH_3\end{array} \xrightarrow[-2H]{-C_6H_5NH_2} C_6H_4\left\langle\begin{array}{l}CH=CH\\ \quad\ |\\ N—CCH_3\end{array}\right.$$

The hydrogen set free sometimes occasions a partial reduction of the reaction product to tetrahydroquinoline derivatives.

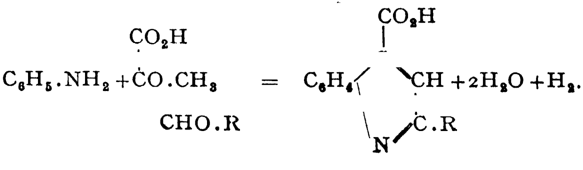
(*b*) Instead of two molecules of the same aldehyde, a mixture of two aldehydes, or an aldehyde with a ketone, may be used; in the latter case α,γ-di- or α,β,γ-trialkylquinolines are formed (C. Beyer, B. **20,** 1908)—*e.g.*:



$$\begin{array}{l}\qquad\quad CH_3\\ \qquad\quad\ |\\ C_6H_5\ \ CO—CH_3\\ \quad\diagdown\\ \quad NH_2 + CHO.CH_3\end{array} \longrightarrow \begin{array}{l}\qquad\quad CH_3\\ \qquad\quad\ |\\ \qquad\quad C=CH\\ C_6H_4\left\langle\begin{array}{l}\\ \quad\ |\\ \end{array}\right.\\ \qquad\quad N=C.CH_3\end{array}$$

α,γ-Dimethylquinoline.

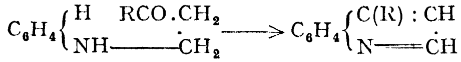
(*c*) *α-Alkylcinchoninic acids* (α-alkylquinoline-γ-carboxylic acids) are produced by the interaction of a mixture of pyroracemic acid and an aldehyde upon aniline (B. **281,** 1):



$$C_6H_5.NH_2 + \begin{array}{l}CO_2H\\ \dot{C}O.CH_3\\ CHO.R\end{array} = C_6H_4\left\langle\begin{array}{l}\ \ CO_2H\\ \quad\ |\\ \quad CH\\ \\ N\ \ C.R\end{array}\right. + 2H_2O + H_2.$$

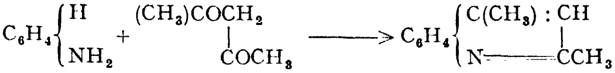
This is a reaction which, particularly when naphthylamine is substituted for aniline, proceeds so smoothly that the production of naphtho-cinchoninic acids may be applied as a test for the *detection of aldehydes in mixtures.* Pyroracemic acid alone, when heated with aniline, yields the α-methylquinoline-γ-carboxylic acid (aniluvitonic acid), together with phenyllutidone; this is because aldehyde is formed from one molecule of the pyroracemic acid.

(*d*) β-Chlorethyl ketones, like $CH_2ClCH_2COCH_3$, give, on heating with aniline and aniline hydrochloride, in the presence of alcohol, γ-alkyl quinolines, with intermediate formation of β-anilino-ethyl ketones:



$$C_6H_4\left\{\begin{array}{ll}H & RCO.CH_2\\ NH & \text{———}CH_2\end{array}\right. \longrightarrow C_6H_4\left\{\begin{array}{l}C(R):CH\\ N=\!=CH\end{array}\right.$$

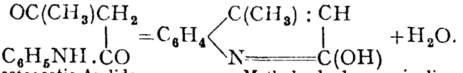
(*e*) β-Diketones, with anilines and dehydrating agents, give quinolines (compare B. **36,** 2448, 4013):



$$C_6H_4\left\{\begin{array}{l}H\\ NH_2\end{array}\right. + \begin{array}{c}(CH_3)COCH_2\\ |\\ COCH_3\end{array} \longrightarrow C_6H_4\left\{\begin{array}{l}C(CH_3):CH\\ \qquad\qquad\ |\\ N=\!=\!=CCH_3\end{array}\right.$$

5. Hydroxyquinoline derivatives are obtained from aniline derivatives of β-ketonic acids and β-dicarboxylic acids by a ring formation (L. Knorr, B. **17,** R. 147; A. **236,** 112).

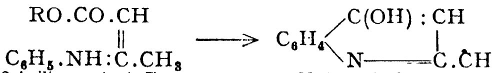
(*a*) Acetoacetic anilide (from aniline and acetoacetic ester when heated to 110°), acted upon with concentrated acids, forms α-hydroxy-γ-methylquinoline (γ-methyl carbostyril) (Knorr, A. **236,** 112):



Acetoacetic Anilide. γ-Methyl-α-hydroxyquinoline.

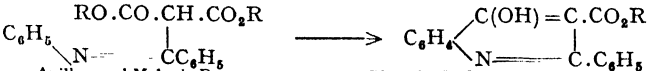
Methyl acetoacetic anilide by the same treatment yields β,γ-dimethyl carbostyril, and acetoacetic methyl anilide gives the methyl derivative of γ-methyl *pseudo*-carbostyril.

(*b*) On the other hand, β-anilino-crotonic ester, formed at the ordinary temperatures, yields γ-hydroxy-α-methylquinoline when heated to 240° (Conrad and Limpach, B. **24,** 2990):



β-Anilino-crotonic Ester. α-Methyl-γ-hydroxyquinoline.

Benzoyl acetic ester, acetone dicarboxylic ester, etc., react similarly. Instead of aniline, homologous anilines, antivanilic acid, or phenylene diamine can be used (B. **31,** 2143; **33,** 3439; **38,** 2044). Benzanilide-imide chloride and sodium malonic ester yield anilbenzoylmalonic ester, which condenses to α-phenyl-γ-hydroxyquinoline-β-carboxylic ester (B. **19,** 1541):



Anilbenzoyl Malonic Ester. α-Phenyl-γ-hydroxyquinoline-β-carboxylic Ester.

Phosphorus pentachloride converts malonanilic acid into *α,β,γ-trichlorquinoline* (B. **18,** 2975; **20,** 1235); the alkyl malonic acids react similarly.

6. The conversion of *indoles* and alkyl indoles into trialkylic *dihydroquinolines*, analogous to that of pyrroles into pyridines by alkyl iodides, has been described above. *β*-Bromo- and chloroquinaldines are produced on heating methylindole with sodium alcoholate and CCl_3H or CBr_3H (B. **21,** 1940). *α*-Methylindole yields quinoline on conducting its vapour through incandescent tubes (B. **38,** 1949).

Behaviour.—The quinoline bases are liquids which dissolve with difficulty in water, readily in alcohol and ether, and possess a penetrating odour. Like the pyridines, they are tertiary bases, and like them form:

1. *Salts* and *double salts* (see mercury salts, B. **28,** R. 617). The platinum double salts are not changed by boiling (*cf.* p. 164).

2. Ammonium- (*quinolinium-*) compounds are formed by their union with alkyl iodides. The additive power for alkyl iodides is, however, limited by the character of the substituents present in the quinolines (B. **24,** 1984). On heating the quinoline iodalkylates, they partly decompose into alkyl iodide and quinoline.

3. Quinoline, like pyridine, is but slightly attacked by nitric acid or chromic acid. Potassium permanganate, however, destroys the benzene nucleus in it, with production of *α,β-pyridinedicarboxylic acid* (quinolinic acid).

The homologous quinolines, containing the alkyl groups in the pyridine nucleus, and those containing the substituents in the benzene nucleus are oxidized by chromic acid in the presence of sulphuric acid, to the corresponding quinoline carboxylic acids, while potassium permanganate, on the other hand, usually oxidizes those substituted in the benzene nucleus, with the formation of *pyridinepolycarboxylic acids* (B. **23,** 2252).

Potassium permanganate converts the *α*-alkylquinolines, by the destruction of their pyridine nucleus, into acid derivatives of *o*-aminobenzoic acid. By this treatment *α*-phenylquinoline yields *benzoyl anthranilic acid* (B. **19,** 1196).

The pyridine nucleus is similarly ruptured by the oxidation of the quinolinium compounds.

4. The pyridine nucleus of the quinolines, when reduced with zinc and hydrochloric acid, takes up four atoms of hydrogen, with the production of tetrahydroquinolines. Decahydroquinoline finally results by more energetic reduction.

The number of known quinoline derivatives is very great. To a certain extent they have a technical value as antiseptics, antipyretics, dyes, etc. Only the more important members of this group will receive consideration in the succeeding paragraphs.

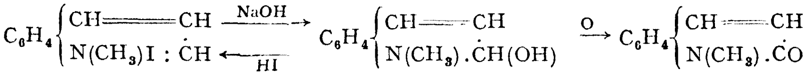
Quinoline, C_9H_7N, is a colourless, strongly refracting liquid, with penetrating odour, which possesses a powerful antiseptic action. It boils at 239°; its sp. gr. = 1·095 at 20°. It occurs in bone-oil and coal-tar. It results when many alkaloids are distilled, and is best prepared synthetically by Skraup's method—*i.e.*, boiling a mixture of 38 grams aniline, 100 grams sulphuric acid, 24 grams nitrobenzene or arsenic acid, and 120 grams glycerol for several hours (B. **14**, 1002; **27**, 574; **29**, 704).

It forms crystalline and very soluble salts with one equivalent of acids; the characteristic bichromate, $(C_9H_7N_2)Cr_2O_7H_2$, dissolves with difficulty and forms yellow needles, melting at 165°.

Quinoline betaïne, $C_9H_7\overline{N.CH_2.CO.O}$, melts at 171°. Its hydrochloride is formed from quinoline and chloracetic acid. *Di-*, *tetra-*, *hexa-*, and *decahydroquinoline* result from the reduction of quinoline.

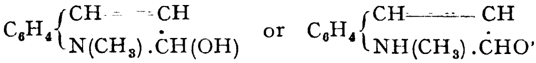
Alkyl-quinolinium Compounds.—**Quinoline-methiodide,** $C_9H_7N.JCH_3 + H_2O$, m.p. 72° (anhydrous, m.p. 133°), **quinoline-ethiodide,** m.p. 159°. The hydroxides soluble in water which are first formed from the alkyl-quinolinium iodides with alkalies are unstable with the exception of the amino- and hydroxy-quinolinium bases. In this respect they resemble the pyridinium hydroxides, and, like the latter, they isomerise into non-conducting α-hydroxy-dihydroquinolines (pseudo-bases), insoluble in water. These also are mostly reactive, and soda converts them by simultaneous processes of oxidation and reduction into *N*-alkyl-α-quinolones and *N*-alkyltetrahydroquinolines; with alkaline solution of potassium ferricyanide nothing but the *N*-alkyl-α-quinolone is produced (A. **282**, 363; B. **36**, 2568).

Acids reconvert them into the original quinolinium salts:



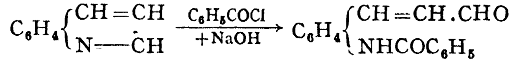
$$C_6H_4\left\{\begin{array}{l}CH{=\!=}CH\\ N(CH_3)I : \dot{C}H\end{array}\right. \underset{HI}{\overset{NaOH}{\rightleftarrows}} C_6H_4\left\{\begin{array}{l}CH{=\!=}CH\\ N(CH_3).\dot{C}H(OH)\end{array}\right. \xrightarrow{O} C_6H_4\left\{\begin{array}{l}CH{=\!=}CH\\ N(CH_3).\dot{C}O\end{array}\right.$$

The α-hydroxydihydroquinolines are distinguished by a remarkable reactivity of the hydroxyl group. Thus, on boiling with alcohols they yield the corresponding alkoxy-compounds or alcoholates. They also expel water and react with aniline, phenylhydrazine, hydroxylamine, and such compounds as contain a methylene group capable of reaction (B. **44**, 680; J. pr. Ch. [2], **84**, 219). For this reason the open formula of the o-alkylamino-cinnamic aldehydes has been considered for the α-hydroxydihydroquinolines:



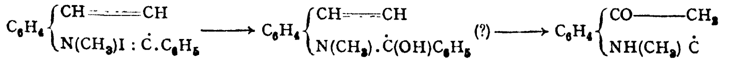
$$C_6H_4\left\{\begin{array}{l}CH{=\!=}CH\\ N(CH_3).\dot{C}H(OH)\end{array}\right. \quad \text{or} \quad C_6H_4\left\{\begin{array}{l}CH{=\!=}CH\\ NH(CH_3).\dot{C}HO\end{array}\right.$$

with the assumption of a ring-splitting, as observed in the case of dinitrophenyl-pyridinium chloride. In some cases the rupture of the quinoline-ring has been proved with certainty. Thus the action of benzoyl-chloride and soda upon quinoline produces o-benzoylamino-cinnamic aldehyde (B. **38**, 3415):



$$C_6H_4\left\{\begin{array}{l}CH=CH\\ N{=\!=}\dot{C}H\end{array}\right. \xrightarrow[+NaOH]{C_6H_5COCl} C_6H_4\left\{\begin{array}{l}CH=CH.CHO\\ NHCOC_6H_5\end{array}\right.$$

The α-phenyl-quinoline-methiodide yields with soda an easily reactive hydroxydihydroquinoline, which is oxidized even in the air to o-methylamino-dibenzoyl-methane (B. **44**, 2670):

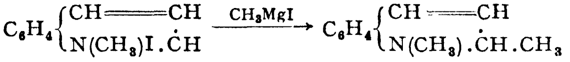


$$C_6H_4\left\{\begin{array}{l}CH{=\!=}CH\\ N(CH_3)I : \dot{C}.C_6H_5\end{array}\right. \longrightarrow C_6H_4\left\{\begin{array}{l}CH{=\!=}CH\\ N(CH_3).\dot{C}(OH)C_6H_5\end{array}\right. (?) \longrightarrow C_6H_4\left\{\begin{array}{l}CO{-\!-}CH_2\\ NH(CH_3)\ \dot{C}\end{array}\right.$$

The great reactive power of the hydroxydihydroquinolines and the condensation power of the methyl group in α- and γ-methyl-quinolines is probably the cause of the formation of the magnificent blue and red dyes of the *cyanines*, iso*cyanines*, and *apocyanines*. The former are obtained by the action of alkali upon mixtures of quinoline-iodalkylates with lepidine- and quinaldine-iodalkylates, while the latter result from treating quinoline-iodalkylates alone with alcoholic potash. These dyes, of as yet unknown constitution, are used in photography as sensitizers for producing ortho-chromatic plates (B. **37,** 2821; **41,** 3054; **44,** 690; J. p. Ch. [2], **73,** 100; **84,** 239).

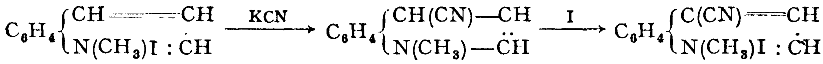
Related to the transposition of the quinolinium hydroxides into hydroxydihydroquinolines are the following transformations of the quinoline-halogen-alkylates:

(*a*) With alkyl-magnesium haloids they produce *N*,α-dialkyl-dihydroquinolines (B. **42,** 1101):



$$C_6H_4\left\{\begin{matrix}CH=\!=\!=CH\\ N(CH_3)I.CH\end{matrix}\right. \xrightarrow{CH_3MgI} C_6H_4\left\{\begin{matrix}CH=\!=\!=CH\\ N(CH_3).\dot{C}H.CH_3\end{matrix}\right.$$

(*b*) With potassium cyanide the transposition of the quinolinium cyanides probably formed in the first instance produces unstable *N*-alkyl-dihydro-cinchoninic acid nitriles which, on oxidation with potassium ferricyanide, pass into *N*-alkyl-γ-cyano-α-quinolones, and by treatment with iodine solution into iodalkylates of the cinchoninic acid nitriles (B. **44,** 2058):



$$C_6H_4\left\{\begin{matrix}CH=\!=\!=CH\\ N(CH_3)I : CH\end{matrix}\right. \xrightarrow{KCN} C_6H_4\left\{\begin{matrix}CH(CN)—CH\\ N(CH_3)—CH\end{matrix}\right. \xrightarrow{I} C_6H_4\left\{\begin{matrix}C(CN)=\!=\!=CH\\ N(CH_3)I : CH\end{matrix}\right.$$

It is remarkable that the action of benzoylchloride and potassium cyanide produces *N*-benzoyl-dihydro-quinaldinic acid nitrile (B. **38,** 1606).

Homologous Quinolines.—The seven isomeric *methylquinolines* are all known. The four quinolines, methylated in the benzene nucleus, sometimes called *toluquinolines* or *methylbenzoquinolines*, are obtained by the reaction of Skraup from the three toluidins: *o*-**methylquinoline** boils at 248°, the *para* at 257°, the *meta* at 248°, and the *ana* at 250°.

α-**Methylquinoline, Quinaldine,** $C_9H_6N(CH_3)$, boiling at 247°, occurs in coal-tar quinoline (25 per cent.) (B. **16,** 1082). It is produced by the various synthetic methods, by the reduction of γ-hydroxyquinaldine, and by fusing ethylacetanilide, $C_6H_5N(C_2H_5).CO.CH_3$, with zinc chloride (B. **23,** 1903). It may also be obtained by digesting aniline, paraldehyde, and crude hydrochloric acid for several hours (B. **16,** 2465). For its salts, see B. **41,** 2701.

β-**Methylquinoline,** $C_9H_6(CH_3)N$ (B. **20,** 1916), boils at 253°, and melts at 10°–14°. It is formed by heating *o*-aminobenzaldehyde with propionic aldehyde to 220° (B. **42,** 1144).

γ-**Methylquinoline, Lepidine,** occurs, together with quinoline and quinaldine, in coal-tar, and is obtained on distilling cinchonine with caustic potash. It may be synthetically prepared. It boils at 257°. Chromic acid oxidizes both methylquinolines to the corresponding quinoline monocarboxylic acids. Potassium permanganate produces pyridine tricarboxylic acids.

α,β-**Dimethylquinoline,** $C_9H_5(CH_3)_2N$, boils at 261° (B. **22,** 267).

α,γ-**Dimethylquinoline,** boiling at 266°, is made from acetyl acetone and aniline, as well as from dihydrotrimethylquinoline, which is produced by the interaction of indole and methyl iodide (*Cf.* pp. 28, 191).

β,γ-**Dimethylquinoline,** from β,γ-dimethyl carbostyril, melts at 65° and boils at 290°. **o-** and **p-Toluquinaldine,** $C_9H_5(CH_3)_2N$ (B. **23,** 3483).

α-**Ethylquinoline,** $C_9H_6(C_2H_5)N$, boils at 255°–260°, β-**Ethylquinoline** at 265°. They result on heating ethyl quinolinium iodide to 250° (analogous to the formation of alkyl pyridines, p. 164). γ-**Ethylquinoline** boils at 270°–275°.

γ-**Propylquinoline,** b.p.$_{16}$ 159°. On trimethylquinolines, see B. **21,** R. 138. β-**Ethyllepidine,** $C_9H_5N[\beta,\gamma](C_2H_5)(CH_3)$, and its derivatives (see B. **31,** 2143).

As in the case of the α- and γ-alkylpyridines, so also in the quinolines, CH_3- and CH_2R-groups in the α- and γ-positions are capable of condensations with aldehydes and phthalic acid anhydrides.

With quinaldine, formaldehyde gives **Methylolquinaldine,** *Quinaldinealkine,* C_9H_6N-α-CH_2CH_2OH, m.p. 105°, **Dimethylolquinaldine,** *Quinolylpropanediol,* $(C_9H_6N)CH(CH_2OH)_2$, m.p. 117°, and **Trimethylolquinaldine,** $(C_9H_6N)C(CH_2OH)_3$, m.p. 143°; but if substitution is in the β-position, the α-methyl group only takes up the two methylol groups, forming β-**methyl-dimethylolquinaldine,** $C_9H_5N[\beta]CH_3[\alpha]CH(CH_2OH)_2$, m.p. 107°. Similarly, lepidine yields, besides **methylollepidine,** $C_9H_6N[\gamma]CH_2CH_2OH$, an oil, only **dimethylollepidine,** $C_9H_6N[\gamma]CH(CH_2OH)_2$, m.p. 128°; in the α,γ-dimethylquinoline only the CH_3-group in the α-position reacts in the first instance. γ-**Methyl methylol-** and **dimethylolquinaldine,** m.p. 98° and 140°; chloral and phthalic acid anhydride (see below) also react with the α-methyl group (B. **37,** 1322). Elimination of H_2O converts quinaldinealkine into α-**vinyl quinoline,** $(C_9H_6N)CH:CH_2$. The quinoline-propanediols, reduced with HI, yield γ- and α-*iso*propyl-quinoline (B. **32,** 223).

According to the conditions, benzaldehyde produces with quinaldine and lepidine either **benzylidin-quinaldine** and **-lepidine,** (C_9H_6N)-α- and -γ-$CH:CHC_6H_5$, m.p. 100° and 92° respectively, or **benzylidene-diquinaldine** and **dilepidine,** $(C_9H_6N.CH_2)_2CHC_6H_5$, m.p. 156° with dec. and 218° respectively. The reduction of benzylidene-quinaldine and -lepidine produces benzyl-quinaldine and -lepidine, m.p. 30° and 101° respectively, which again can combine with 2 or 1 molecule formaldehyde (B. **32,** 3599).

With chloral, lepidine condenses to **lepidine chloral,** $(C_9H_6N)CH_2CH(OH)CCl_3$, m.p. 175°, and, with special readiness, quinaldine to **quinaldine chloral,** C_9H_6N-α-$CH_2CH(OH)CCl_3$, m.p. 144°, which, with alkali, yields α-**quinolyllactic acid,** $(C_9H_6N)CH_2CH(OH)COOH$, and α-**quinolyl acrylic acid,** $(C_9H_6N)CH:CHCOOH$. With concentrated sulphuric acid, quinolyllactic acid gives **quinolylacetaldehyde,** $(C_9H_6N)CH_2CHO$, m.p. 104°, and by oxidation, α-**quinolyl-acetic acid,** $(C_9H_6N)CH_2COOH$, m.p. 275°. Chloral lepidine with alkali gives **quinolyl-γ-acrylic acid,** m.p. 250°–255° with dec., which, on reduction with HI and P, gives **quinolyl-γ-propionic acid,** m.p. 203° (B. **37,** 1337).

On heating with phthalic acid anhydride to 220°, quinaldine yields a yellow dye called **quinophthalone,** $(C_9H_6N)CH<^{CO}_{CO}>C_6H_4$, m.p. 241°. At a lower temperature the isomeric **quinaldylidene phthalide** or iso*quino-phthalone,* $(C_9H_6N)CH:\overline{C.C_6H_4COO}$, m.p. 187°, is formed, which is converted into quino-phthalone on heating to 250° or treating with sodium ethylate (B. **37,** 3006). Compare the conversion of benzylidenephthalide into phenyl-diketohydrindene.

Quino-phthalono-sulphonic acid is called *Quinoline Yellow,* a silk and wool dye. For quinaldine and phthal-aldehydic acid, see B. **29,** 187.

With oxalic ester and potassium ethylate, quinaldine and lepidine condense to the yellow **quinaldineoxalic ester** and **lepidineoxalic ester,** $(C_9H_6N)CH : C(OH)CO_2C_2H_5$, m.p. 131° and 195°, which in alkalies form a yellow solution, but in acids a colourless solution, probably with conversion into the keto-form (B. **42,** 1140).

α-Phenylquinoline, $C_9H_6(C_6H_5)N$, is obtained from cinnamic aldehyde and aniline upon heating them with hydrochloric acid to 200°. It melts at 84° and boils at 363°. Potassium permanganate oxidizes it to benzoylanthranilic acid. **β-Phenylquinoline** is an oil, which solidifies on cooling (B. **16,** 1836).

γ-Phenylquinoline is formed from its acid. It melts at 61°. It is closely related to the quinia alkaloids (B. **20,** 622). See B. **27,** 907, for **γ-Quinolyl phenols.**

Nitrophenylquinoline, $NO_2C_6H_4.C_9H_6N$, melting at 159°, is formed from *iso*diazonitrobenzene and quinoline (B. **29,** 168).

γ-Phenyl-α-methylquinoline, *γ-phenylquinaldine,* $C_9H_5(C_6H_5)(CH_3)N$, results by the condensation of benzoylacetone with aniline (B. **20,** 1771). It melts at 99° and yields γ-phenylquinoline-α-carboxylic acid when its phthalone is oxidized with chromic acid. This new acid affords γ-phenylquinoline.

α-Phenyl-γ-methylquinoline is produced (B. **19,** 1036) by distilling flavenol with zinc dust. It melts at 65°.

Its *p*-amino-derivative, **Flavaniline,** applied as a beautiful yellow dye (B. **15,** 1500), is **α-Aminophenyl-γ-methylquinoline,** $C_9H_5(CH_3)(C_6H_4NH_2)N$. It results in the condensation of *o*-aminoacetophenone and *p*-aminoacetophenone when digested with zinc chloride (B. **19,** 1038). Its monacid salts are yellow in colour, and have been used as dyes (B. **15,** 1500). Nitrous acid converts it into so-called **Flavenol,** $C_9H_5(C_6H_4OH)(CH_3)N$, **α,*p*-Hydroxyphenyl-γ-methylquinoline.** On *o*-flavaniline, see B. **32,** 3231.

Various isomeric **diquinolyls,** $(C_9H_6N)_2$, have been prepared by boiling quinoline with sodium; further, by conducting its vapours through tubes heated to redness, and finally from benzidine and other diaminodiphenyls through Skraup's quinoline synthesis (M. **8,** 121; B. **17,** 1965; B. **20,** 634; B. **38,** 762; A. **287,** 38, etc.).

Diquinolylquinoline, $C_9H_7N.C_9H_6N.C_9H_7N$, melting at 151°, is formed from γ-acetacetyl quinolin, $C_9H_7N.COCH_2COCH_3$, with two molecules of *o*-amino-benzaldehyde (B. **29,** R. 845).

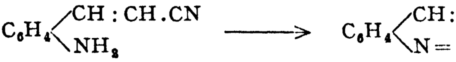
Triquinolylmethane, $CH(C_9H_6N)_3$, melting at 202°, is obtained from pararosaniline by the reaction of Skraup (B. **24,** 1606, 2267).

Halogen, Sulpho-, and Nitro-Derivatives of the Quinolines.—All those containing the substituents in the benzene nucleus are prepared by the methods in use for the introduction of such groups into benzene and naphthalene. Or the corresponding substituted benzene derivatives are subjected to the quinoline syntheses given above. It is more difficult to introduce the halogens, the nitro- or the sulpho-groups into the pyridine nucleus of quinoline. *Py*-Chlorine derivatives of quinoline are chiefly made by the action of PCl_5 upon *Py*-hydroxyquinolines. α-Chloroquinolines are also formed from *N*-alkyl-α-quinolones with phosphorus chlorides (B. **32,** 1297; **35,** 3678). The ready mobility of the halogen atoms occupying the α- or γ-positions in quinoline is very remarkable. They can be easily replaced by OH, NHR, etc.

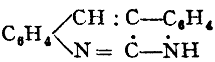
α-Chloroquinoline, C_9H_6ClN, melting at 38° and boiling at 267°, is prepared from carbostyril, *N*-methyl- or *N*-ethyl-quinolone, and PCl_5 (B. **15,** 333). **β-Chloroquinoline,** boiling at 255°, is produced from quinoline and sulphur chloride along with the compound called thioquinanthrene, $(C_9H_5N)_2S_2$, and trichloroquinoline (B. **29,** 2456). **α-Bromoquinoline** melts at 49° (J. pr. Ch. [2], **41,** 41). **β-Bromoquinoline,** melting at 13° and boiling at 276°, results from the action of sulphur bromide upon quinoline or by heating quinoline hydrochloride with bromine (B. **27,** R. 732; **25,** R. 422; **29,** 2459). **γ-Chloroquinoline,** melting at 34°, is obtained from kynurine and also from γ-aminoquinoline (B. **27,** R. 748). **γ-Bromoquinoline** results when PBr_5 acts upon kynurine (B. **27,** R. 732). **α-Iodoquinoline iodomethylate,** $C_9H_6IN.ICH_3$, melting at 212°, is produced when methyl iodide acts upon α-chloroquinoline (A. **282,** 376). **α-Methyl-β-chloroquinoline,** melting at 72°, is produced from methylindole, CCl_3H, and sodium alcoholate (B. **21,** 1942). **α,β-Dichloroquinoline,** melting at 105°, results in the action of PCl_5 upon hydrocarbostyril. **α,β,γ-Trichloroquinoline,** $C_9H_4Cl_3N$, melting at 107°, is formed from malonanilic acid and PCl_5 (B. **17,** 737) (II. 108).

Amino-quinolines, substituted in benzene nucleus, are produced in the reduction of the corresponding nitroquinolines. The *Py*-α- and γ-amino-quinolines result upon heating α- or γ-chloro- (bromo-) quinolines with amines or ammonia.

α-Amino-quinolines are also obtained by synthesis from *o*-amino-cinnamic acid nitriles (B. **32,** 3399):



$$C_6H_4\left\langle\begin{matrix}CH:CH.CN\\NH_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH:CH\\N=CNH_2\end{matrix}\right.$$

—see also the formation of the so-called quindoline,  $C_6H_4\left\langle\begin{matrix}CH:C—C_6H_4\\N=C—NH\end{matrix}\right.$ —by reduction of *oo′*-**dinitro-cyano-dibenzyl,** $NO_2C_6H_4CH_2CH(CN)$-$C_6H_4NO_2$.

α-Aminoquinoline, $(C_9H_6N)NH_2$, m.p. 120°, from cinnamic acid nitrile with sodium ethylate (see above), from α-chloroquinoline, on heating with ammonia and ammonium carbonate to 200° (besides carbostyril), and by reducing disintegration of α-phenyl-hydrazido-quinoline or hydrazoquinoline (see below) (J. pr. Ch. [2], **56,** 204; B. **31,** 1297), is hydrolyzed by conc. alkalies into NH_3 and carbostyril; its *methiodide*, m.p. 247°, is also obtained from α-iodoquinoline-methiodide with NH_3 (A. **282,** 380). α-**Anilinoquinoline,** $(C_9H_6N).NHC_6H_5$, m.p. 98°, from α-chloroquinoline and aniline at 200°.

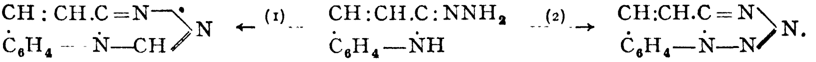
α-**Amino**-β-**phenylquinoline,** $(C_9H_5N)(NH_2)(C_6H_5)$, m.p. 156° (corr.), is obtained on reducing α-phenyl-*o*-nitrocinnamic acid nitrile, or on condensing *o*-acetamino-benzaldehyde with benzyl cyanide.

β-**Aminoquinoline,** $(C_9H_6N)NH_2$, dimorphous, m.p. 84° and 94°, from β-quinoline-carboxylic acid amide with NaOBr (C. 1910, I. 2102). β-**Aminoquinaldine,** m.p. 160°, is formed by Beckmann's transposition from the oxime of β-acetylquinaldine (B. **40,** 3425).

γ-**Aminoquinoline,** $(C_9H_6N)NH_2 + H_2O$, m.p. 70° (anhydrous 154°), is formed from cinchoninic acid amide with bromine and alkali (J. pr. Ch. [2], **56,** 181).

γ-**Aminoquinaldine,** $C_9H_5(CH_3)N(NH_2)$, m.p. 270° (B. **21,** 1980). *p*-**Methoxy**-γ-**aminoquinoline,** $C_9H_5(OCH_3)N(NH_2)$, m.p. 120°, from quinic acid amide with KOBr (B. **29,** R. 674).

Quinolyl Hydrazines are obtained from the α- and γ-chloro-quinolines by heating with hydrazine or phenylhydrazines (B. **24,** 2817; **33,** 1885). α-**Quinolylhydrazine,** $(C_9H_6N).NH.NH_2$, m.p. 135°, in certain reactions behaves as a hydrazidine, giving the so-called *naphtriazole* (1), m.p. 175°, with formic acid, and *naphtetrazole* (2), m.p. 157°, with nitrous acid:



$$\begin{array}{l}CH:CH.C{=}N{-}\\ \dot{C}_6H_4{-}\dot{N}{-}CH\end{array}\!\!>\!N \xleftarrow{(1)} \begin{array}{l}CH:CH.C:NNH_2\\ \dot{C}_6H_4{-}\dot{N}H\end{array} \xrightarrow{(2)} \begin{array}{l}CH:CH.C{=}N\\ \dot{C}_6H_4{-}\dot{N}{-}N\end{array}\!\!>\!N.$$

The naphtetrazole is quantitatively converted into tetrazole by oxidation with $KMnO_4$ (B. **33,** 1890).

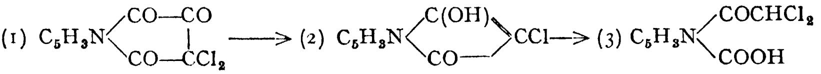
α-**Lepidylhydrazine,** $[C_9H_5(CH_3)N]NHNH_2$, m.p. 146°. γ-**Quinaldylhydrazine,** m.p. 118°, α-**Hydrazoquinoline,** $(C_9H_6N)NH.NH(C_9H_6N)$, m.p. 229°, and α-**hydrazolepidine,** m.p. 265°, are formed, besides the hydrazines, on heating the α-chloroquinolines with hydrazine hydrate. On oxidation they give α-**azo-quinoline** and **-lepidine,** m.p. 230°, and 235° respectively, and by reduction with zinc dust and HCl α-amino-quinoline and -lepidine.

α-**Benzenehydrazoquinoline,** $(C_9H_6N)NHNHC_6H_5$, m.p. 191°, gives on oxidation **benzeneazoquinoline,** m.p. 93° (B. **24,** 2817).

Hydroxyquinolines.—The hydroxyquinolines manifest the character both of bases and of phenols. Those containing the hydroxyl in the benzene nucleus, called also quinophenoles or oxybenzoquinolines, are synthesized from the three aminophenols by Skraup's and Döbner-Miller's reactions; also by reduction of the *Bz*-nitroquinolines, or from the quinoline sulphonic acids by fusion with caustic potash (B. **28,** R. 912). Into the hydroxyquinolines thus obtained further hydroxyl groups can then be introduced by fusion with potash.

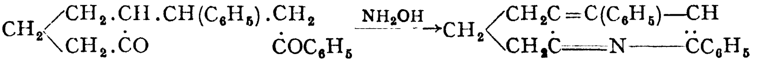
1-**Hydroxyquinoline,** $C_6H_3(OH):(C_3H_3N)$, is most readily prepared from 1-quinoline sulphonic acid (B. **16,** 712). It melts at 75° and boils at 266°. From it is obtained 1-**Ethoxy**-4-**acetaminoquinoline,** ***analgene,*** $C_6H_2(OC_2H_5)(NH.COCH_3):(C_3H_3N)$, melting at 155°, which has been recommended for the alleviation of pain. *p*-**Hydroxyquinoline,** m.p. 194°, is also formed from xanthoquinic acid by rejection of CO_2; the iodoalkylates of *p*-hydroxyquinoline yield stable quinolinium hydroxides, while the *p*-alkoxy-quinolines behave in this matter like the other quinoline derivatives (B. **36,** 456, 1169). **Loretin,** used as a substitute for iodoform, is an ***m*-iodo-*o*-hydroxyquinoline-*a*-sulphonic acid,** $C_6H(OH)I(SO_3H)(C_3H_3N)$ (J. pr. Ch. [2], **55,** 457).

The *Bz*-hydroxyquinolines, when acted upon in glacial acetic acid solution with chlorine (Zincke's method), are converted, like the naphthols, into chlorinated quinoline-quinones, which (similarly to the conversion of naphthalene derivatives into indenes) are rearranged to **pyrindene** derivatives of a condensed pyridine and *cyclo*pentene ring. Thus from *p*-hydroxyquinoline and chlorine by various transformations of the primary reaction-products, **dichlorotriketotetrahydroquinoline** (1) results. This, on boiling with water, becomes ***β*-chloro-*a*-oxypyrindone** (2), from which **dichloracetopicolinic acid** (3) is obtained by rupture of the ring (A. **290,** 321):



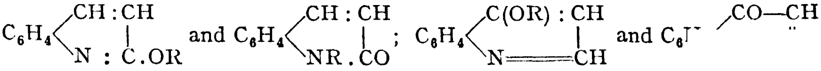
$$(1)\ C_5H_3N\left\langle\begin{matrix}CO-CO\\ |\\ CO-CCl_2\end{matrix}\right. \longrightarrow (2)\ C_5H_3N\left\langle\begin{matrix}C(OH)\\ CO\end{matrix}\right\rangle CCl \longrightarrow (3)\ C_5H_3N\left\langle\begin{matrix}COCHCl_2\\ COOH\end{matrix}\right.$$

Pyrindene derivatives have also been obtained by syntheses: **Diketo-hydropyrindenecarboxylic ester,** $C_5H_3N\left\{\begin{matrix}[a]CO\\ [\beta]CO\end{matrix}\right\rangle CHCO_2CH_3$, from quinolinic acid ester with acetic ester and sodium (B. **35,** 1411). ***β*-Phenyl-diketo-hydropyrindene,** $C_5H_3N\left\{\begin{matrix}[\beta]CO\\ [\gamma]CO\end{matrix}\right\rangle CHC_6H_5$, by transposition from the *benzylidene cinchomeronide*, $\overline{OCOC_5H_3NC} : CHC_6H_5$, the condensation product of cinchomeronic acid anhydride with phenyl-acetic acid (B. **37,** 2137). ***aγ*-Diphenyl-hydropyrindene,** from the diketone resulting from the addition of *cyclo*-pentanone to benzalacetophenone on treatment with hydroxylamine (B. **35,** 3973):



$$CH_2\left\langle\begin{matrix}CH_2.CH.CH(C_6H_5).CH_2\\ CH_2.CO\qquad\qquad COC_6H_5\end{matrix}\right. \xrightarrow{NH_2OH} CH_2\left\langle\begin{matrix}CH_2C=C(C_6H_5)-CH\\ CH_2C=\!=N=\!=CC_6H_5\end{matrix}\right.$$

The hydroxyquinolines with hydroxyl in the pyridine nucleus are feebler bases and phenols than the *Bz*-Hydroxyquinolines. As in the case of the oxypyridines or pyridones, it is undetermined whether the hydroxyl or keto-form should be given to the oxyquinolines of the *a*- and *γ*-positions. Ethers, however, of the two forms—*e.g.*, *carbostyril* and pseudo*carbostyril*—exist:



$$C_6H_4\left\langle\begin{matrix}CH:CH\\ |\\ N:C.OR\end{matrix}\right. \text{ and } C_6H_4\left\langle\begin{matrix}CH:CH\\ |\\ NR.CO\end{matrix}\right. ;\ C_6H_4\left\langle\begin{matrix}C(OR):CH\\ |\\ N=\!=\!=CH\end{matrix}\right. \text{ and } C_6\ \ \begin{matrix}CO-CH\end{matrix}$$

For syntheses of *Py*-hydroxyquinolines, see above.

***a*-Hydroxyquinoline, Carbostyril,** $C_9H_7ON(+H_2O)$, the lactim or lactam of *o*-amino-cinnamic acid, is most readily obtained by the reduction of *o*-nitro-cinnamic ester (B. **14,** 1916). It may also be prepared from *o*-acetamino-benzaldehyde, $C_6H_4\left\langle\begin{matrix}CHO\ CH_3\\ |\\ NH-CO\end{matrix}\right.$, with caustic soda (C. 1900, II. 427); from *a*-chloroquinoline by heating it with water, and by digesting quinoline with a bleaching lime solution (B. **21,** 619). It melts at 199°.

Water decomposes its salts with alkalies and acids. Potassium permanganate oxidizes it to oxalylanthranilic acid, $C_6H_4<\begin{matrix}COOH\\NH.CO.CO_2H\end{matrix}$. Sodium and alcohol reduce it to tetrahydroquinoline.

Carbostyril methyl ether, boiling at 247°, and the *ethyl ether*, boiling at 256°, or *a-methoxy-* and *ethoxy-quinolines*, are oils. They are produced by the action of the alkyl iodides upon the Na- or Ag-salts of carbostyril, by the action of sodium alcoholates upon α-chlorquinolines, and when *o*-aminocinnamic esters are digested with alcoholic zinc chloride.

The pseudo*carbostyril ethers*—the *methyl*, melting at 71°, and the *ethyl*, at 54°, otherwise *N*-methyl- and *N*-ethyl-α-quinolone—are produced by the action of the alkyl iodides upon free carbostyril in the presence of alkalies. Also when sodium hydroxide acts upon methyl- and ethyl-quinolinium iodide. *N*-Methylquinolone is also produced when ethoxyquinoline is heated with methyl iodide (B. **30,** 930). With P_2S_5 it yields *N*-methylthio-quinolone, $C_9H_6SN(CH_3)$, m.p. 118° (B. **33,** 3358).

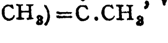
1-**Nitrocarbostyril,** $C_9H_6(NO_2)ON$, melting at 168°, results from the action of alcoholic ammonia upon nitrocoumarin. 3-**Hydroxycarbostyril,** melting beyond 300°, is formed by the condensation of 6-amino-*m*-hydroxycinnamic acid, which is produced in the electrolytic reduction of *o*-nitrocinnamic acid. β-**Hydroxyquinoline,** $(C_9H_6N)OH$, m.p. 198°, from diazotated β-aminoquinoline (C. 1910, I. 2103). β-**Hydroxyquinaldine,** $C_9H_5(CH_3)N[\beta]OH$, has been prepared by the condensation of *o*-aminobenzaldehyde and chloracetone with NaHO (B. **35,** 2554).

γ-**Methyl-α-hydroxyquinoline,** γ-**Methylcarbostyril,** or **Lepidone,** $C_9H_6(CH_3)ON$, melting at 223° and boiling at 270° (17 mm.), is obtained from acetoacetanilide. Its lactime ether, *a-Methoxy-γ-methylquinoline*, boiling at 276°, results when $NaOCH_3$ acts upon α-chlorlepidine. The lactam ether, *N-methyl lepidone*, melting at 131°, is prepared from acetoacetic ester and methylaniline, and by heating ethoxylepidine with methyl iodide (B. **30,** 931).

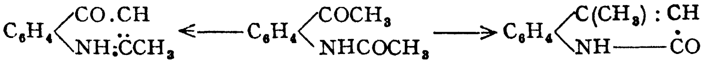
Bz-**Amino-lepidone,** m.p. 270°, from *m*-phenylene diamine and aceto-acetic ester (B. **31,** 798).

Dilepidone, $[C_9H_5(CH_3)ON]_2$, is formed from benzidine and aceto-acetic ester.

γ-**Hydroxyquinoline, Kynurine,** $C_9H_7ON(+3H_2O)$, is made by heating kynurenic acid (hydroxyquinolinecarboxylic acid), and by oxidizing cinchonine and cinchoninic acid with chromic acid (B. **22,** R. 758). It melts at 201°. PCl_5 converts it into γ-chloroquinaldine (B. **27,** R. 748), from which sodium methylate produces γ-**methoxyquinoline,** m.p. 31°, b.p. 245°; the latter, also obtained from kynurine and diazomethane, on heating to 300° to 310°, transposes into *N*-**methyl-γ-quinolone,** m.p. 143° (M. **27,** 255).

γ-**Hydroxy-α-methylquinoline,** γ-**Hydroxyquinaldine,** γ-**quinaldone,** $C_9H_6(CH_3)ON(+2H_2O)$, m.p. 231°, from aceto-acetic ester, anil also gives two isomeric ethers, γ-**methoxyquinaldine,** b.p. 298°, and *N*-**methyl quinaldone,** m.p. 175° (B. **22,** 78); both ethers give, with methyl iodide, the same iodo-methylate,  $C_6H_4\begin{matrix}\diagup C(OCH_3)=CH\\ \diagdown N(ICH_3)=\dot{C}.CH_3\end{matrix}$, which, on heating or treatment with alkalies, gives *N*-methyl quinaldone (B. **30,** 922); compare the similar behaviour of the antipyrines, pyridones, etc.

The two isomers, quinaldone and lepidone, are also produced together from *o*-acetamino-acetophenone with NaHO:



$$C_6H_4\left\langle\begin{matrix}CO.CH\\ NH{:}\ddot{C}CH_3\end{matrix}\right. \longleftarrow C_6H_4\left\langle\begin{matrix}COCH_3\\ NHCOCH_3\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}C(CH_3):CH\\ NH\text{——}\dot{C}O\end{matrix}\right.$$

Similar reactions are shown by *o*-propiono- and *o*-butyr-amino-acetophenones; *o*-acetamino-benzo-phenone gives **α-oxy-γ-phenyl quinoline,** m.p. 259°.

***p*,γ-Dihydroxy-quinoline,** $C_9H_7O_2N$, is formed by the saponification of *p*-methoxy-kynurine, produced from *p*-methoxy-γ-amino-quinoline with nitrous acid (B. **29,** R. 675).

α,γ-Dihydroxy-quinoline, γ-Hydroxy-carbostyril, $C_9H_7O_2N$, subliming, is formed from γ-bromocarbostyril with potash; from *o*-amino-phenyl propiolic acid by heating with SO_4H_2; by the condensation of anthranilic acid ester and acetic ester with sodium (B. **32,** 3570); or from *o*-acetanthranilic acid ester by means of sodium (C. 1900, I. 427; 1901, I. 236). With diazonium salts it combines to form fast azo-dyestuffs (C. 1906, I. 109). Reduction of its β-nitroso derivative produces **αβγ-trihydroxy-quinoline,** $C_9H_7O_3N$, which is oxidized by ferric chloride to quinisatinic acid and quinisatin or triketo-tetrahydroquinoline (B. **17,** 985).

Thiolquinoline, $(C_9H_6N)SH$, m.p. 175°, and ***p*-methylthiolquinoline,** m.p. 210°, from α-chloroquinoline and α-chlorotoluquinoline, with KSH (B. **32,** 1305); ***N*-methylthiolquinoline** is obtained from methyl carbostyril (see above).

Quinoline Aldehydes and Ketones.—*o*-**Quinoline-aldehyde,** $CHO.C_6H_3[C_3H_3N]$, m.p. 95° (see B. **38,** 1280). **α-Quinoline aldehyde,** $C_9H_6(CHO)N$, m.p. 71°, is formed from α-quinolyl acrylic acid with $KMnO_4$; its oxime, m.p. 189°, from *o*-amino-benzaldehyde with *iso*-nitroso-acetone by method 2 (J. pr. Ch. [2], **66,** 264).

A **nitro-γ-quinoline aldehyde,** $(NO_2)C_9H_5(CHO)N$, m.p. 175°, is obtained from nitro-dibromo-lepidine, $(NO_2)C_9H_5(CHBr_2)N$, with lead acetate (B. **31,** 2368).

Py-Quinoline ketones are produced by synthetic method 2 from *o*-amino-benzaldehyde and β-diketones:

β-Acetylquinaldine, $C_9H_5(CH_3)(COCH_2)N$, melts at 57·5° (B. **25,** 1756.)

β-Acetylcarbostyril, $C_9H_6(COCH_3)ON$, melting at 232°, is formed from *o*-amino-benzaldehyde and acetoacetic ester (B. **16,** 1838).

γ-Acetacetylquinoline, $C_9H_7N(CO.CH_2.CO.CH_3)$, melting at 65° and boiling at 206° (17 mm.), is prepared from cinchoninic ester, acetone, and sodium ethylate. It condenses with phenylhydrazine to *phenylquinolylmethylpyrazole*, melting at 120°, and with two molecules of *o*-amino-benzaldehyde to *diquinolyl quinoline* (B. **29,** R. 845).

Quinoline Carboxylic Acids.—They exhibit the character of amino-acids. Those substituted in the benzene nucleus have been synthesized from the amino-benzoic acids (B. **28,** 2809), and are produced when

Bz-alkyl quinolines are treated with chromic acid. The *Py*-quinoline carboxylic acids also result from the action of a chromic acid mixture upon *Py*-alkyl quinolines. The alkyl groups in the γ-position are most easily oxidized, the β- with more difficulty, and the alkyl groups in the α-position with the greatest difficulty (B. **23,** 2254) (p. 544). When they are heated, carbon dioxide is expelled and the respective quinolines are produced. The acids, carrying the carboxyl in the α-position, are coloured reddish-yellow by ferrous sulphate.

o-**Quinolinecarboxylic acid,** $C_9H_6N(COOH)$, melts at 187°. The *meta*-acid melts at 248°–250°. The *para*-acid melts at about 291°. The *ana*-acid melts at 360° (A. **237,** 325; B. **19,** R. 443, 548; **43,** 3026).

α-**Quinolinecarboxylic acid, Quinaldinic acid,** crystallizes from hot water in needles containing $2H_2O$; it melts at 156°, and decomposes. It is obtained from quinaldine, or, better, from the condensation products of quinaldine with formaldehyde (B. **39,** 2329). On heating with acetic or benzoic acid anhydride it splits off CO_2 and turns into a red substance very sensitive to light (B. **38,** 2127). Quinaldinic acid chloride, m.p. 97° (B. **39,** 2330).

β-**Quinolinecarboxylic acid** is also produced by heating *acridic acid.* It melts at 273° (B. **18,** 1640).

γ-**Quinolinecarboxylic acid, cinchoninic acid,** was first produced upon oxidizing cinchonine with potassium permanganate or nitric acid. It contains 1 or $2H_2O$. It melts at 254°. Synthetically it has been produced by the condensation of isatinic acid, acetaldoxime, and NaHO (J. pr. Ch. [2], **66,** 263). Chloride, m.p. 170° (C. 1901, I. 1052). Its nitrile, m.p. 95°, is formed from the *N*-methyl-dihydro-cinchoninic acid nitrile, the transformation product of quinoline methiodide with KCN, by oxidation with alcoholic iodine solution and disintegration of the resulting cinchoninic acid nitrile methiodide by heating (B. **44,** 2058). The acid easily yields quinoline; $KMnO_4$ oxidizes it to αβγ-pyridine tricarboxylic acid. Nitro-sulphuric acid nitrates cinchoninic acid to *ana*-nitro-cinchoninic acid, which is reduced by ammonium sulphide to *ana*-amino-cinchonic acid. This acid easily yields an anhydride, $C_9H_5N\begin{cases}[4]NH\\ \quad\dot{}\\ [\gamma]CO\end{cases}$, m.p. 255° (B. **32,** 717), analogous to *peri*-naptho-styril.

Alkyl cinchoninic acids are produced by the condensation of aldehydes with pyro-racemic acid and anilines (B. **22,** R. 23; **42,** 4072; A. **281,** 1); also from isatinic acid, $C_6H_4\left\langle\begin{matrix}COCOOH\\ NH_2\end{matrix}\right.$, by method 2 (J. pr. Ch. [2], **56,** 283; **57,** 467; **66,** 263).

α-**Methylcinchoninic acid,** *Aniluvitoninic acid,* $C_9H_5(CH_3)(COOH)N(+H_2O)$, m.p. 242°, is formed from pyro-racemic acid and aniline (B. **20,** 1769), and from isatinic acid and acetone. α-**Phenyl cinchoninic acid,** m.p. 209°, from aniline, benzaldehyde, and pyro-racemic acid, or isatinic acid and acetophenone, is recommended under the name Atophane as an antineuralgic and a remedy for gout. β-**Methyl** and β-**phenylcinchoninic acid,** m.p. 254° and 273°, from isatinic acid with propionaldoxime and phenylacetaldoxime respectively (B. **39,** 982; **40,** 1088). αβ-**Diphenyl-** and **-dimethylcinchoninic acid,** m.p. 295° and 316° with dec. (J. pr. Ch. [2], **56,** 283).

α-Methylquinoline-β-carboxylic acid, Quinaldine-β-carboxylic acid, m.p. 234° with dec., is formed from *o*-amino-benzaldehyde with aceto-acetic ester (J. pr. Ch. [2], **56,** 373).

γ-Methylquinoline-α-carboxylic acid, Lepidine-α-carboxylic acid, m.p. 153°–154°, from γ-methylmethylolquinaldine by oxidation and rejection of CO_2 (B. **37,** 1322).

Acridinic acid, α,β-Quinoline-dicarboxylic acid, $C_9H_5N(COOH)_2$, is produced when acridine is oxidized with potassium permanganate, just as quinoline yields α,β-pyridinedicarboxylic acid. It crystallizes in needles with $2H_2O$, or plates with $1H_2O$, and decomposes at 120°–130°.

α,γ-Quinolinedicarboxylic acid results when α-cinnamenyl-cinchoninic acid is oxidized with potassium permanganate (B. **22,** 3009). It melts at 246° with decomposition (B. **22,** 3009). It is also formed from isatinic acid with pyro-racemic acid (J. pr. Ch. [2], **56,** 308).

Quinaldine-β,γ-dicarboxylic acid, $C_9H_4(CH_3)N(COOH)_2$, from isatinic acid and aceto-acetic ester. The following are produced similarly: **α-Phenyl-βγ-quinolinedicarboxylic acid,** $C_9H_4(C_6H_5)N(COOH)_2$, with benzoyl acetic ester, **quinaldine-βγ-aceto-carboxylic acid,** $C_9H_4(CH_3)N(CH_2COOH)(COOH)$, with lævulinic acid, and others (J pr. Ch. [2], **57,** 467).

Hydroxyquinoline Carboxylic Acids :

α-Hydroxyquinoline-β-carboxylic acid, $C_9H_5(OH)(COOH)N$, results in the condensation of *o*-amino-benzaldehyde with malonic acid, and melts above 320°.

α-Hydroxyquinoline-γ-carboxylic acid is formed on melting cinchoninic acid with potash. It melts at 310° and decomposes. It is obtained by fusing cinchoninic acid with potash and by internal condensation of *N*-acetyl isatinic acid, $C_6H_4<{COCOOH \atop NHCOCH_3}$ (C. 1900, I. 427). Both acids decompose into CO_2 and carbostyril on heating their silver salts.

Kynurenic Acid is a *γ-hydroxyquinoline-β-carboxylic acid.* It occurs in the urine of dogs after the ingestion of meat. It is also formed in the transformation of the primary disintegration product of albumen called tryptophane (Z. physiol. Ch. **43,** 325), and has been obtained synthetically from *o*-formyl-amino-phenyl-propiolic acid ester by boiling with NaHO (B. **34,** 2703). It contains $1H_2O$, and melts at 257°. Fusion with caustic potash converts it into CO_2 and kynurine or γ-hydroxyquinoline; on oxidation it yields kynuric acid or oxalyl anthranilic acid.

***p*-Hydroxyquinoline-γ-carboxylic Acid,** $C_9H_5(OH)N(CO_2H)(+H_2O)$, *Xanthoquinic acid,* results on fusing *para*sulphocinchoninic acid with KOH. It melts at 320° with decomposition. Its *methyl ether,* **quinic acid,** $C_9H_5(O.CH_3)N(CO_2H)$, is obtained by oxidizing quinine and quinidin with chromic acid in sulphuric acid solution. It melts at 280°.

γ-Hydroxyquinaldine-β-carboxylic Acid, $C_9H_4(CH_3)ON(COOH)$, melting at 245° with decomposition, results in the condensation of anthranilic acid with acetoacetic ester (B. **27,** 1396).

α-Hydroxyquinoline-γ-acetic acid, $(C_9H_6ON)CH_2COOH$, m.p. 206° with dec., is obtained by the condensation of acetone dicarboxylic acid anilide with sulphuric acid ; ***Bz*-amino-α-hydroxyquinoline-γ-acetic acid** is formed similarly (B. **33,** 3439).

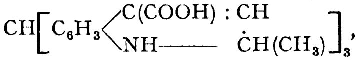
HYDROQUINOLINES.

Dihydro-quinolines have hitherto only been obtained in bimolecular or polymolecular form in the reduction of quinolines with zinc dust and HCl, besides the tetrahydroquinolines (B. **44,** 2106). In this form they are not further reducible to tetrahydroquinolines, but they easily pass into the corresponding quinolines on oxidation with HgO, CrO_2, etc.

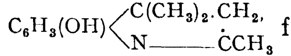
Dihydroquinaldine, $[C_9H_8N(CH_3)]_2$, m.p. 178°; **o-Toludihydroquinoline,** m.p. 144°; **o-Toludihydroquinaldine,** m.p. 217°.

N,*a*-**Dialkyl-** and *N*,*a*,*a*-**Trialkyl-Δ,*β*-dihydroquinolines** are formed by the action of alkyl magnesium haloids upon the quinoline iodo-alkylates. They are mono-molecular, and are reduced by tin and HCl to tetrahydroquinolines (B. **42,** 1101).

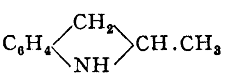
N-**Methyl-*a*-methyl-** and *N*-**methyl-*a*-ethyldihydroquinoline,** b.p. 258° and 266°. *N*-**Methyl-*a*-phenyldihydroquinoline,** m.p. 90°, yields with MnO_4K *n*-methyl benzoyl anthranilic acid; *N*,*a*-**dimethyldihydroquinaldine,** b.p. 274°.

Other dihydroquinolines must be assumed as intermediate products in the quinoline ring syntheses according to the method of Döbner and v. Miller, which, however, cannot as a rule be isolated on account of their instability. On condensing anilines with pyro-racemic acid and adding formaldehyde, derivatives of dihydro-*a*-methylcinchoninic acid are obtained, the so-called *hydro-glauconinic acids*, of the probable structure,  $CH\left[C_6H_3\begin{matrix}\diagup C(COOH):CH\\ \diagdown NH\text{———}\dot{C}H(CH_3)\end{matrix}\right]_3$, which in alkaline solution are converted into **glauconinic acids,** blue mordant dyes, by oxidation in air. Their structure recalls that of the triphenyl-methane dyes (compare B. **31,** 686; **33,** 677).

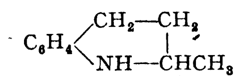
On *Bz*-**Hydroxy-*a*,*γ*,*γ*-trimethyl-dihydro-quinoline,**

 $C_6H_3(OH)\begin{matrix}\diagup C(CH_3)_2.CH_2,\\ \diagdown N\text{———}\dot{C}CH_3\end{matrix}$ from *m*-aminophenol and mesityl oxide, see B. **32,** 3701.

Tetrahydroquinolines.—These are produced when the quinolines are reduced with tin and hydrochloric acid, or with sodium and alcohol. The pyridine nucleus then takes up four hydrogen atoms. This procedure changes the chemical nature of the quinolines very materially. *The tetrahydroquinolines behave like secondary fatty-aromatic amines.* Nitrous acid converts them into *N*-nitrosamines, which readily rearrange themselves to *Bz*-*p*-nitrosamines. With the salts of diazobenzene they yield diazoamino-compounds, which readily pass over into *p*-azobenzene derivatives. This alteration in the chemical character of quinoline is similar to that seen in the indoles by their change to dihydroindoles. The tetrahydroquinolines are to be regarded as ring homologues of the dihydroindoles:



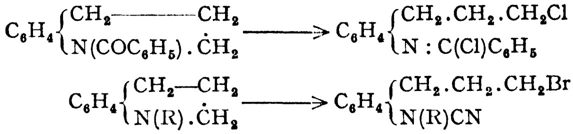
Dihydromethylindole.



Tetrahydroquinaldine.

whereas the basal substances, the indoles and the quinolines, behave very differently. The tetrahydroquinolines are oxidized to quinolines again by iodine, chromic acid, silver acetate, or $Hg(NO_3)_2$ (B. **27,** 824; C. 1900, I. 137).

Like piperidine, tetrahydroquinoline can be split up into derivatives of *o*-propyl aniline by treating its *N*-benzoyl compounds with PCl_5, or by the action of cyanogen bromide upon its *N*-alkyl derivatives (B. **37,** 2921; **42,** 2219):

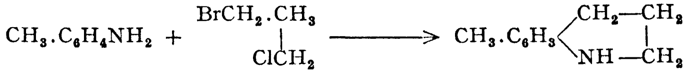


$$C_6H_4\left\{\begin{matrix}CH_2\text{———}CH_2\\ N(COC_6H_5).CH_2\end{matrix}\right.\longrightarrow C_6H_4\left\{\begin{matrix}CH_2.CH_2.CH_2Cl\\ N:C(Cl)C_6H_5\end{matrix}\right.$$

$$C_6H_4\left\{\begin{matrix}CH_2\text{—}CH_2\\ N(R).CH_2\end{matrix}\right.\longrightarrow C_6H_4\left\{\begin{matrix}CH_2.CH_2.CH_2Br\\ N(R)CN\end{matrix}\right.$$

Tetrahydroquinoline, $C_9H_{11}N$, boiling at 244°, is liquid at the ordinary temperature. It is formed when tin and hydrochloric acid act upon quinoline and *α*- and *γ*-chlorquinolines; also by the action of sodium and alcohol upon carbostryril (B. **23,** 1142). Nitrous acid converts it into a *nitroso*-body, which is easily rearranged to p-*nitrosotetrahydroquinoline,* melting at 134° (B. **16,** 732). With benzoyl chloride it forms n-*benzoyltetrahydroquinoline,* melting at 75°; with methyl iodide, ***N*-Methyltetrahydroquinoline, kairoline,** $C_9H_{10}N.CH_3$, boiling at 245°, which is said to have the same action as **kairine** (a febrifuge), the hydrochloride of ***o*-hydroxy-*N*-methyltetrahydroquinoline,** $C_9H_9(OH)N.CH_3$, melting at 114°, and **thalline,** the sulphate of ***p*-methoxytetrahydroquinoline,** $C_9H_9(OCH_3)NH$, melting at 42° and boiling at 283°, and possessing the action of a febrifuge.

Tetrahydrotoluquinoline, $CH_3.C_6H_3:[C_3H_7N]$, boiling at 257°, is produced on boiling toluidine with trimethylene chlorobromide (B. **24,** 2061; **25,** 2805):



$$CH_3.C_6H_4NH_2 + \begin{matrix}BrCH_2.CH_3\\ |\\ ClCH_2\end{matrix}\longrightarrow CH_3.C_6H_3\left\langle\begin{matrix}CH_2\text{—}CH_2\\ |\\ NH\text{—}CH_2\end{matrix}\right.$$

The *nitroso*-compound melts at 51°; the *benzene-diazo*-body at 99°.

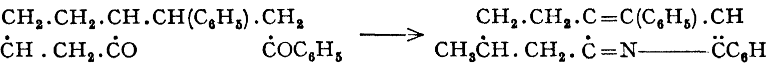
Tetrahydroquinaldine, $C_6H_4\left\langle\begin{matrix}CH_2\text{—}CH_2\\ NH\text{—}CHCH_3\end{matrix}\right.$, b.p. 247°, is also formed by the reduction of *o*-nitrobenzyl acetone, $C_6H_4<\begin{matrix}NO_2\\ CH_2CH_2COCH_3\end{matrix}$ (B. **14,** 890). Tetrahydroquinaldine possesses an asymmetric C-atom, and has been split up by means of its bitartrate and bromo-camphor sulphonate into two optically active components (B. **41,** 966; C. 1911, I. 162).

A few quaternary tetrahydroquinolinium bases, with two different radicals like alkyl kairolinium hydroxide, $C_9H_{10}N(CH_3)(C_3H_5)OH$, have been split up through their *d*-camphor sulphonates and *d*-bromo-camphor sulphonates into *optically active nitrogen compounds* (B. **38,** 1840; **40,** 4450).

The δ-lactams of *o*-aminophenyl fatty acids—*e.g.*, **Hydrocarbostyril,** or *o*-amino-phenyl-propionic acid lactam—are keto-derivatives of tetrahydroquinoline. Hydrocarbostyril has been obtained by the Beckmann rearrangement of *α*-hydrindone oxime, as well as from its acid, ***β*-hydrocarbostyril carboxylic acid,** $C_9H_{10}NO(COOH)$, melting at 146° with decomposition. Its ester results in the reduction of nitrobenzyl malonic ester (B. **29,** 665). **Quinisatin,** or *o*-amino-benzoyl glyoxylic acid lactam, is *triketotetrahydroquinoline.*

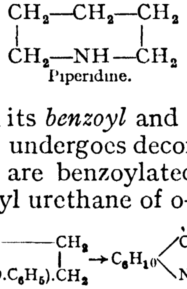
Tetrahydroquinoline-*Bz*-carboxylic acids (see B. **35,** 2611).

A derivative of *Bz*-tetrahydroquinoline has been obtained by boiling the diketone produced by the condensation of benzal-acetophenone with 2-methyl-cyclohexanone, with hydroxylamine hydrochloride (B. **35,** 3978):



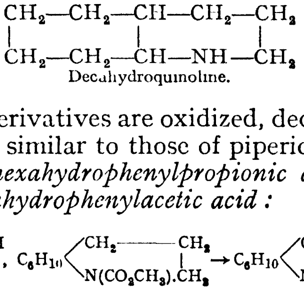
$$\begin{array}{l}\mathrm{CH_2.CH_2.CH.CH(C_6H_5).CH_2}\\ \mathrm{CH_3\dot{C}H\,.\,CH_2.\dot{C}O}\qquad\qquad \mathrm{\dot{C}OC_6H_5}\end{array}\longrightarrow\begin{array}{l}\mathrm{CH_2.CH_2.C{=}C(C_6H_5).CH}\\ \mathrm{CH_3\dot{C}H.\,CH_2.\,\dot{C}{=}N\text{———}\ddot{C}C_6H_5}\end{array}$$

Hexa- and Decahydroquinolines.—When quinoline or tetrahydroquinoline is heated to high temperatures with hydriodic acid and phosphorus, or with hydrogen at 110 atmospheres pressure in the presence of nickel oxide to 240° (B. **41,** 992), the benzene nucleus also takes up hydrogen, and the reaction product yields, in addition to a little **hexahydroquinoline,** $C_9H_{13}N$, boiling at 226° (B. **27,** 1459), and other products, **decahydroquinoline,** $C_9H_{18}N$, melting at 48° and boiling at 204°. It is a very volatile, strongly alkaline substance, which has a stupefying odour like that of coniine. While tetrahydroquinoline resembles the mixed fatty aromatic bases, decahydroquinoline manifests the properties of a secondary amine of the aliphatic series. *It is the piperidine of the quinoline group :*



$$\begin{array}{ccc}\mathrm{CH_2}—&\mathrm{CH_2}—&\mathrm{CH_2}\\ |&&|\\ \mathrm{CH_2}—&\mathrm{NH}—&\mathrm{CH_2}\end{array}$$

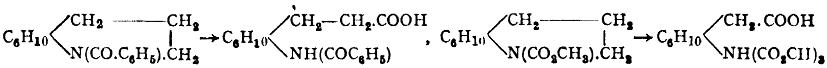
Piperidine.



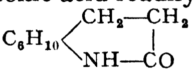
$$\begin{array}{ccccc}\mathrm{CH_2}—&\mathrm{CH_2}—&\mathrm{CH}—&\mathrm{CH_2}—&\mathrm{CH_2}\\ |&&|&&|\\ \mathrm{CH_2}—&\mathrm{CH_2}—&\mathrm{CH}—&\mathrm{NH}—&\mathrm{CH_2}\end{array}$$

Decahydroquinoline.

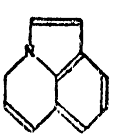
When its *benzoyl* and *urethane* derivatives are oxidized, decahydroquinoline undergoes decompositions similar to those of piperidine; the products are benzoylated *o-aminohexahydrophenylpropionic acid* and the methyl urethane of *o-aminohexahydrophenylacetic acid :*



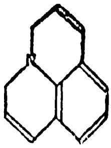
$$\mathrm{C_6H_{10}}\!\left\langle\begin{array}{l}\mathrm{CH_2\text{———}CH_2}\\ \mathrm{N(CO.C_6H_5).CH_2}\end{array}\right.\!\rightarrow \mathrm{C_6H_{10}}\!\left\langle\begin{array}{l}\mathrm{CH_2{-}CH_2.COOH}\\ \mathrm{NH(COC_6H_5)}\end{array}\right.,\ \mathrm{C_6H_{10}}\!\left\langle\begin{array}{l}\mathrm{CH_2\text{———}CH_2}\\ \mathrm{N(CO_2CH_3).CH_2}\end{array}\right.\!\rightarrow \mathrm{C_6H_{10}}\!\left\langle\begin{array}{l}\mathrm{CH_2.COOH}\\ \mathrm{NH(CO_2CH_3)}\end{array}\right.$$

Free *o*-aminohexamethylenepropionic acid readily parts with water and becomes **Decahydrocarbostyril,**  $\mathrm{C_6H_{10}}\!\left\langle\begin{array}{l}\mathrm{CH_2{—}CH_2}\\ \quad\ \ |\\ \mathrm{NH{—}CO}\end{array}\right.$ (B. **27,** 1458).

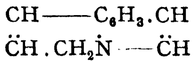
Julole and **lilole** compounds are derivatives of hydroquinolines. They are probably derived from the hypothetical parent substances:



Lilole.



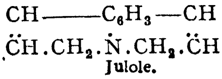
Julole.



$$\begin{array}{l}\mathrm{CH\text{———}C_6H_3.CH}\\ \mathrm{\ddot{C}H\,.\,CH_2\dot{N}\,\text{——}\ddot{C}H}\end{array}$$

Lilole.

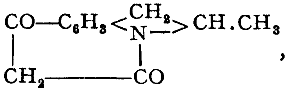
and

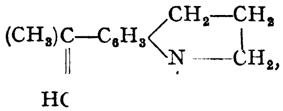


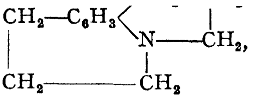
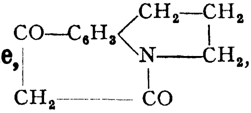
$$\begin{array}{l}\mathrm{CH\text{———}C_6H_3—CH}\\ \mathrm{\ddot{C}H.CH_2.\dot{N}.CH_2.\ddot{C}H}\end{array}$$

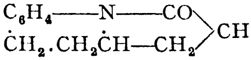
Julole.

Lilole must be considered as a combination of the quinoline nucleus with the pyrrole nucleus, or of the pyridine nucleus with the indole nucleus, while julole is a combination of the quinoline nucleus with the pyridine nucleus.

Diketomethyllilolidine, 
$$\begin{array}{lll} CO-C_6H_3<\overset{CH_2}{N-}>CH.CH_3 \\ | \qquad\qquad\quad | \\ CH_2 \text{———} CO \end{array}$$
, is obtained from malonic ester and dihydromethylindole. It has been described in connection with the latter.

Ketomethyljuloline,  melting at 130°, is formed from tetrahydroquinoline and acetoacetic ester (B. **24,** 845).

Julolidine,  melting at 40°, is produced on boiling tetrahydroquinoline with one molecule of trimethylene chlorobromide, or aniline with two molecules of trimethylene chlorobromide (B. **25,** 2801). Both julole derivatives are bases, whereas **diketojulolidine,**  obtained from tetrahydroquinoline and malonic ester, has only acid properties.

A similar combination is contained in **tetrahydroquinolyl-α-propionic acid lactam,** 
$$\begin{array}{l} C_6H_4\text{——}N\text{——}CO \\ CH_2.CH_2CH\text{—}CH_2 \end{array}>CH_2$$
m.p. 116°. The tetrahydroquinolyl propionic acid and the lactam are obtained by the reduction of quinolyl-α-acrylic acid with Na and alcohol. It recalls strychnine in many ways (B. **33,** 218). See also piperolidone.

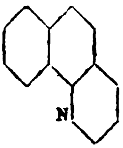
III. CONDENSED QUINOLINES.

Condensations similar to those effected through aniline in the quinoline syntheses can be carried out with the higher aromatic amines—*e.g.*, naphthylamine, anthramine, the aminoquinolines, the phenylenediamines, etc. All these amines yield with glycerol (Skraup), or with aldehydes, etc. (Döbner-Miller, p. 189), higher condensed bases containing the quinoline nucleus.

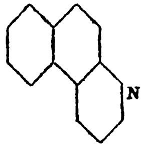
In these reactions the pyridine ring, as a rule, then attaches itself only to two such members of the benzene nucleus, which, according to the requirements of the Kekulé formula, are doubly linked (B. **26,** R. 402; **27,** R. 631). This would argue against the various centric and diagonal formulas which have been suggested for the derivatives of benzene and of pyridine.

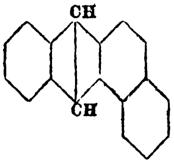
A and B.—The two naphthylamines give rise to α- and β-naphthoquinoline (I. and II.) (constitution, see J. pr. Ch. [2], **57,** 85); amino-anthracenes give rise to anthraquinolines (III.).

I.



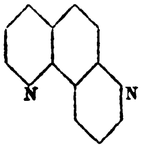
II.



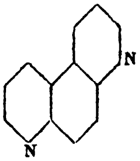


C and D.—*m*- and *p*-phenylene diamines, and *m*- and *p*-amino-quinolines, give rise to phenanthrolines (I.) and *pseudo*-phenanthrolines (II.); a third isomeric phenanthroline (III.) is obtained from *o*-amino-quinoline. The three isomerides might be suitably distinguished as *m*-, *p*-, and *o*-phenanthroline respectively; a fourth isomer, quino-γ-pyridine (IV.), is formed from γ-amino-quinolines.

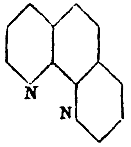
I.



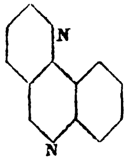
II.



III.



IV.

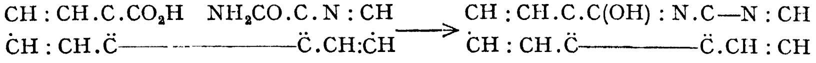


On a fifth isomeride, *iso*quino-β-pyridine, see below. In their behaviour all these bases resemble the quinolines.

A. **α-Naphthoquinoline,** $C_{13}H_9N$, melts at 52° and boils at 251°. **β-Napthhoquinoline** melts at 93°. The latter is obtained from the β-naphthylamines substituted in the α-position by bromine or NO_2, through the splitting-off of the substituents. Potassium permanganate converts the naphthoquinolines into two phenylpyridinedicarboxylic acids.

Amination and subsequent oxidation with $KMnO_4$ convert α-naphthoquinoline into quinoline-1,2-dicarboxylic acid, and β-naphthoquinoline into quinoline-2,3-dicarboxylic acid (C. 1907, I. 637). For derivatives, see J. pr. Ch. [2], **57,** 49.

The monamide of β-phenylpyridinedicarboxylic acid, treated with Br solution, produces **hydroxy-*iso*quino-β-pyridine,**



$$\begin{array}{l} CH:CH.C.CO_2H \quad NH_2CO.C.N:CH \\ \dot{C}H:CH.\ddot{C}\text{———————}\ddot{C}.CH:\dot{C}H \end{array} \longrightarrow \begin{array}{l} CH:CH.C.C(OH):N.C\text{—}N:CH \\ \dot{C}H:CH.\ddot{C}\text{—————}\ddot{C}.CH:CH \end{array}$$

which, on reduction with HI and phosphorus, yields *iso***quinopyridine,** $C_{12}H_8N_2$, m.p. 114°, b.p. above 360° (B. **35,** 296).

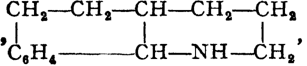
The hydride products of the napthoquinolines are noteworthy. By reduction with Sn and hydrochloric acid the pyridine nucleus, as in the case of quinoline, is hydrogenated.

Tetrahydro-(α)-naphthoquinoline, $C_{10}H_6\Big\langle_{NH—CH}^{\quad\ |}$, melting at 46°, and the *β-body*, melting at 63°, behave like *alkylic* *α-* and *β-naphthylamines*. Sodium and boiling amyl alcohol produce *ar*-**Octohydro-**

$$CH_2—CH_2\diagdown \qquad \diagup CH_2—CH_2$$

melting at 48° and

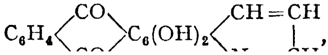
boiling at 216° (37 mm.), and the *β-compound*, melting at 60° and boiling at 325° (717 mm.). In these bodies not only the pyridine nucleus, but also the outer benzene nucleus, has taken up hydrogen atoms, which accounts for their *aromatic benzene amine*—alkylic aniline—*character*. From β-naphthoquinoline there is simultaneously formed an isomeric *ac*-**Octohydro-(β)-naphthoquinoline,**



$$\begin{array}{lllll} CH_2 - & CH_2 - & CH - & CH_2 - & CH_2 \\ | & & | & & | \\ C_6H_4 - & & CH - & NH - & CH_2 \end{array}$$

, melting at 91° and boiling at 321°, in which the middle benzene nucleus is hydrogenated. It therefore corresponds to decahydroquinoline and possesses the properties of a piperidine.

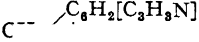
B. **Anthraquinoline,** $C_{17}H_{11}N$, melts at 170° and boils at 446°. Its solutions exhibit an intense blue fluorescence. Chromic acid oxidizes it to **anthraquinone quinoline,** corresponding to anthraquinone. Its dihydroxy-compound is the so-called Alizarin Blue (A. **201,** 349). The isomeric α-**anthraquinonequinoline,** m.p. 169°, can be obtained from α-amino-anthraquinone with glycerin and SO_4H_2 (C. 1908, I. 76), while β-amino-anthraquinone in this reaction produces benzanthrone and **benzanthronequinoline,** $C_{20}H_{11}ON$, m.p. 251°, both of which, on fusion with alkali, are converted into an eminently fast blue-violet vat dye called **cyanthrene** (B. **38,** 194; C. 1906, II. 573). **Alizarin Blue, Dihydroxyanthraquinonequinoline,**



$$C_6H_4\left\langle\begin{array}{c}CO\\ \end{array}\right\rangle C_6(OH)_2\left\langle\begin{array}{l}CH=CH\\ \qquad\ \ |\end{array}\right.$$

, melting at 270°. It consists of metallic, bluish-violet coloured needles. It is produced when β-nitro-alizarin or amino-alizarin is heated with glycerol and sulphuric acid (B. **18,** 445; **29,** 708). It unites with acids and bases to form salts. It occurs in trade in the form of a bluish-violet paste, and, like alizarin, is applied in dyeing. Since reducing agents decolorize it (zinc dust, grape sugar) and it again separates on exposure to the air, it is adapted to vat dyeing.

By the action of sulphuric acid more hydroxyl groups are introduced into alizarin blue. The products are *alizarin blue green, alizarin green, alizarin indigo blue*. These are mixtures of sulpho-acids of tri-, tetra-, and penta-hydroxyanthraquinonequinolines (B. **26,** R. 711). In connection with anthraquinoline, **fluorenequinoline,**



$$C\begin{array}{l}\diagup C_6H_2[C_3H_3N]\\ \end{array}$$

m.p. 133°, and 9,10-**phenanthroquinoline,** $C_{17}H_{16}N$, m.p. 174°, are to be mentioned. They result from 2-amino-fluorene and 9-amino-phenanthrene respectively by Skraup's quinoline synthesis (B. **35,** 3275; **41,** 1998).

C. (*m*)-**Phenanthroline,** $C_{12}H_8N_2(+2H_2O)$, melting at (65°) 78°, is obtained from *meta*-diaminobenzene or 2-aminoquinoline (B. **16,** 2519; **23,** 1016). *p*-**Phenanthroline,** *Pseudo***phenanthroline,** is derived from 3-aminoquinoline, *p*-diaminobenzene, or aminoazobenzene with glycerol and sulphuric acid. It melts at 173°. Potassium permanganate oxidizes the phenanthrolines to α,β- and β,β-dipyridyl dicarboxylic acids (B. **23,** 2623; **42,** 2612).

Phenyl-*m*- and *p*-phenanthroline carboxylic acid, from *m*- and *p*-aminoquinoline with benzaldehyde and pyro-racemic acid (B. **33,** 2918, 2928).

α-Methyl-*o*-phenanthroline, $C_{12}H_7(CH_3)N_2(+2H_2O)$, melting at (53°) 76°, is prepared from 1-amidoquinaldine (B. **22,** 253).

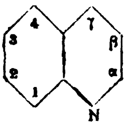
In connection with the phenanthrolines we may mention *phenotripyridine,* $C_6(C_3H_3N)_3$, m.p. 236°, formed by attaching three pyridine nuclei to a benzene nucleus; this very stable compound results from 1,3,5-triamino-benzol by Skraup's quinoline synthesis (Bull. soc. Ch. [3], **13,** 28).

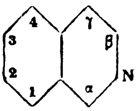
D. **α-Methyl-γ-quinoquinoline,** $C_{12}H_7(CH_3)N_2$, melting at 206° and boiling at 360°, is prepared from γ-amidoquinaldine, glycerol, sulphuric acid, and nitrobenzene (B. **27,** R. 632).

IV. *ISO*QUINOLINE GROUP.

While quinoline or benzopyridine results from pyridine by the attachment of the benzene nucleus to its carbon atoms occupying the α,β-positions, the formula of the isomeric *iso*quinoline or *iso*benzopyridine is produced by the benzene nucleus joining itself to the β,γ-C-atoms of pyridine. Its *nitrogen* member is therefore separated from the benzene nucleus by a methine group:

Quinolin





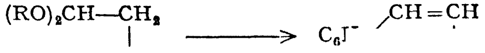
Isoquinolin

This constitution seems evident from the oxidation of *iso*quinoline to β,γ-pyridinedicarboxylic acid, as well as from the methods by which it is obtained synthetically.

Quinoline is similar to *iso*quinoline in its deportment. It is found with it in coal-tar (Hoogewerff and van Dorpp, 1885). It is the mother substance of a class of important alkaloids belonging to the opium bases—*e.g., papaverine, narcotine, hydrastine,* etc.

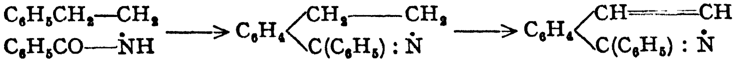
Syntheses of iso*quinoline Derivatives.*—1. *iso*Quinolines are formed by ring completion from benzene derivatives of the constitutions $C_6H_5—C—N—C—CO$ and $C_6H_5—C—C—N—CO$.

(*a*) *iso*Quinoline is formed from benzylidene amino-acetal or benzyl amino-acetaldehyde by heating with H_2SO_4 (B. **27,** R. 628; **28,** 764; compare B. **42,** 2374):



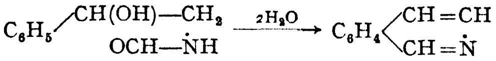
Benzylidene-amino-acetal. *Iso*quinoline.

(*b*) From acylated ω-phenyl ethylamines, by splitting off water with P_2O_5 in boiling toluene or xylene solution, dihydro-*iso*quinolines are formed, which can be oxidized to *iso*quinolines by means of $KMnO_4$ in acid solution (B. **42,** 1973, 2075; C. 1912, I. 1267):



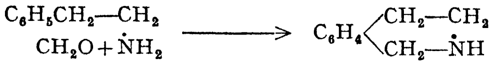
$$\begin{matrix}C_6H_5CH_2—CH_2\\C_6H_5CO—\dot{N}H\end{matrix} \longrightarrow C_6H_4\begin{cases}CH_2——CH_2\\C(C_6H_5):\dot{N}\end{cases} \longrightarrow C_6H_4\begin{cases}CH=\!=\!=CH\\C(C_6H_5):\dot{N}\end{cases}$$

Similarly, *iso*quinolines are obtained direct from acylated aminophenyl carbinols of the formula $C_6H_5CH(OH)CH_2NHCOR$ by means of P_2O_5 (B. **43**, 2384):



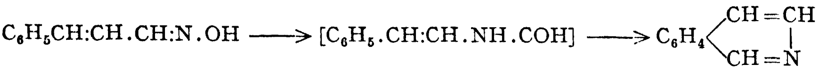
$$C_6H_5\left\langle\begin{array}{l}CH(OH)-CH_2\\ OCH-\dot{N}H\end{array}\right. \xrightarrow{2H_2O} C_6H_4\left\langle\begin{array}{l}CH=CH\\ CH=\dot{N}\end{array}\right.$$

*Tetrahydro-*iso*quinolines*, on the other hand, are formed by the condensation of ω-phenyl ethylamines with aldehydes (B. **44**, 2030):

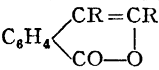


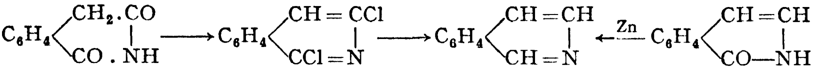
$$\begin{array}{l}C_6H_5CH_2-CH_2\\ CH_2O+\dot{N}H_2\end{array} \longrightarrow C_6H_4\left\langle\begin{array}{l}CH_2-CH_2\\ CH_2-\dot{N}H\end{array}\right.$$

(*c*) Some interest attaches to the formation of *iso*quinoline from cinnamic aldoxime, and from benzylidene acetoxime by heating with P_2O_5 (B. **27**, 2795; **28**, 818). We must here assume an atomic displacement analogous to Beckmann's transformation:



$$C_6H_5CH{:}CH.CH{:}N.OH \longrightarrow [C_6H_5.CH{:}CH.NH.COH] \longrightarrow C_6H_4\left\langle\begin{array}{l}CH=CH\\ \quad\;|\\ CH=N\end{array}\right.$$

2. The linking oxygen atom in the lactones of the formula  $C_6H_4\left\langle\begin{array}{l}CR=CR_1\\ \quad\;|\\ CO-O\end{array}\right.$, so-called *iso*coumarins, can readily be exchanged for the NH-group by means of cold aqueous ammonia. The products are *iso*quinolines or *iso*carbostyrils, which by successive treatment with PCl_5 and HI and phosphorus, or with zinc dust, are converted into *iso*quinolines. Homophthalides and homologous homophthalides, under similar treatment, are also changed to *iso*quinolines (B. **21**, 2299; **25**, 1138, 1493, 3563; **26**, 1842):



$$C_6H_4\left\langle\begin{array}{l}CH_2.CO\\ \quad\;|\\ CO.NH\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}CH=CCl\\ \quad\;|\\ CCl=N\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}CH=CH\\ \quad\;|\\ CH=N\end{array}\right. \xleftarrow{Zn} C_6H_4\left\langle\begin{array}{l}CH=CH\\ \quad\;|\\ CO-NH\end{array}\right.$$

Homo-phthalimide. α,β-Dichlor*iso*quinoline. *Iso*quinoline. *Iso*-carbostyril.

*iso***Quinoline,** C_9H_7N, melting at 23° and boiling at 240·5°, is very similar to quinoline. It occurs, together with ordinary quinoline, in the crude quinoline from coal-tar. It is separated from the accompanying compounds by the crystallization of the sulphates (B. **18**, R. 384). In addition to the methods given above it is also produced by distilling benzylidine ethylamine, $C_6H_5.CH{:}N.CH_2.CH_3$, through tubes heated to redness (B. **25**, 734). Potassium permanganate oxidizes it to phthalic acid (destroying the pyridine nucleus) and β,γ-pyridine dicarboxylic acid (by destroying the benzene nucleus).

Alkylic phthalic acid imides are produced from the halogen alkyl addition products of isoquinolin (B. **21**, R. 786).

Its *methiodide*, $C_9H_7N.ICH_3$, melts at 159°, and its *ethiodide* at 148°. The iodalkylates of *iso*quinoline resemble in their transformations the pyridinium and quinolinium iodides. With NaHO they first form the unstable *iso*quinolinium hydroxide and then α-hydroxydihydro-*iso*quinolines, which are oxidized to *N*-alkyl-α-*iso*quinolones by alkaline potassium ferricyanide solution. With alkyl magnesium haloids they yield *N*,α-dialkyl hydro-*iso*quinolines. *Iso*quinoline betaïne (see C. 1902, II. 1326).

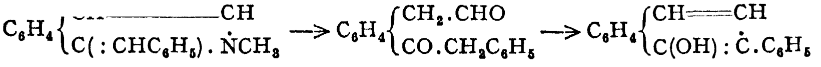
Nitration of *iso*quinoline produces a *Bz*-nitro-*iso*quinoline, m.p. 110° (B. **29,** R. 792). 2,3-**Methylenedioxy-*iso*quinoline,** $(CH_2O_2)C_6H_2(C_3H_3N)$, m.p. 124°, from piperonal amino-acetal, on reduction yields tetrahydro-2,3-methylenedioxy-*iso*quinoline or hydrohydrastinine (A. **286,** 1). 3,4-**Dimethoxy-*iso*quinoline,** $(CH_3O)_2C_6H_2(C_3H_3N)$, m.p. 94°, has been obtained by the action of concentrated H_2SO_4 and arsenic acid upon veratal amino-acetal. It is also produced by the breaking up of *papaverine* on fusion with alkali (B. **42,** 2374).

Bz-1- and 3-**Methyl*iso*quinolines,** boiling at 258° and melting at 83°, and boiling at 264°, are prepared from *o*- and *p*-methylbenzylidene amino-acetal (C. 1897, I. 865).

α-**Methyl*iso*quinoline,** $C_9H_6(CH_3)N$, boiling at 248° (its *sulphate* at 247°), results from the action of sulphuric acid upon acetophenone amino-acetal (B. **27,** R. 628), and from acetamino-methylphenyl carbinol with P_2O_5 (B. **43,** 2389). It is probably identical with the methyl*iso*quinoline isolated from *papaveroline* (B. **23,** R. 653). β-**Methyl*iso*quinoline,** melting at 68° and boiling at 246°, is produced when methyl *iso*carbostyril is distilled with zinc dust. γ-**Methyl*iso*quinoline,** boiling at 256°, is formed when dimethylhomophthalimide is distilled with zinc dust (B. **21,** 2300). β-**Ethyl*iso*quinoline,** $C_9(C_2H_5)H_6N$, boiling at 256°, and β-**Phenyl*iso*quinoline,** $C_9(C_6H_5)H_6N$, melting at 104°, are obtained from ethyl- and phenyl-*iso*carbostyril (B. **25,** 3573; **27,** 2237). α-**Phenyl*iso*quinoline,** melting at 88°, is derived from benzophenoneimino-acetal, $(C_6H_5)_2C : NCH_2CH(OC_2H_5)_2$ (C. 1897, I. 865); or from benzoylamino-methyl phenyl carbinol with P_2O_5 (B. **43,** 2388); and from its dihydro-compound with MnO_4K (B. **42,** 1976).

γ-**Benzyl*iso*quinoline,** $(C_9H_6N)CH_2C_6H_5$, m.p. 118°, b.p.$_{23}$ 238°, is formed, together with a little β-**benzyl*iso*quinoline,** m.p. 104°, b.p.$_{23}$ 311°, by heating tetrahydro*iso*quinoline with benzaldehyde; γ-benzyl *iso*quinoline on oxidation yields pyridine-ββ'γ-tricarboxylic acid. α-**Benzyl*iso*quinoline,** m.p. 55°, b.p.$_{23}$ 228°, is formed from *iso*quinoline and benzyl alcohol by heating; from phenacetylamino-methyl-phenyl-carbinol with P_2O_5 (B. **43,** 2387); and from its dihydro-compound (B. **42,** 1978). It is oxidized to pyridine-αβγ-tricarboxylic acid, and is the foundation body for various alkaloids such as papaverine (B. **33,** 1719; A. **326,** 261; **328,** 326). The iodomethylate of α-benzyl*iso*quinoline yields with soda, instead of the oxy-dihydro-base, the yellow *N*-**methyl-α-benzylidenedihydro*iso*quinoline,** which is also obtained by the action of $C_6H_5CH_2MgCl$ upon *N*-methyl-α-*iso*quinolone; with HI it regenerates the iodo-methylate of α-benzyl*iso*quinoline (B. **37,** 3396).

On prolonged boiling of α-benzyl*iso*quinoline iodo-methylate with NaHO, it splits off methylamine, and passes into β-**phenyl-α-naphthol,** a process which only becomes intelligible on the supposition of a splitting of the ring of the primarily formed *N*-methyl-α-benzylidene dihydro*iso*quinoline (A. **362,** 305):



$$C_6H_4\begin{cases}CH\text{———}CH\\ C(:CHC_6H_5).\dot{N}CH_3\end{cases} \longrightarrow C_6H_4\begin{cases}CH_2.CHO\\ CO.CH_2C_6H_5\end{cases} \longrightarrow C_6H_4\begin{cases}CH{=\!=}CH\\ C(OH):\dot{C}.C_6H_5\end{cases}$$

A beautiful red dye—**Quinoline Red**—is produced by condensing benzotrichloride with quinaldine and *iso*quinoline when they are heated with zinc chloride. This compound has a constitution analogous to that of malachite green (B. **20,** 4).

In addition to its colouring properties, it possesses the remarkable power of rendering photographic plates orthochromatic.

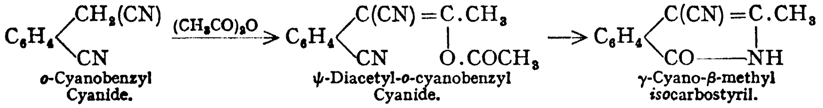
*iso*Quinolines, with halogens in the pyridine nucleus, result when PCl_5 acts upon the *iso*carbostyrils (below) and homophthalimides. Chlorine atoms in the α-position have the same reactivity as the chlorine atoms in the α- or γ-position of quinoline.

α-Chlor*iso*quinoline, C_9H_6ClN, m.p. 38°, b.p. 275°, is formed from *iso*carbostyril with $POCl_3$ (B. **33,** 985). **β-Chlor*iso*quinoline,** m.p. 48°, b.p. 281°, is formed by the partial reduction of **αβ-dichlor*iso*quinoline,** $C_9H_5Cl_2N$, m.p. 122°, b.p. 306°, which is formed from homophthalimide with $POCl_3$ (B. **19,** 2355). **αγ-Dichlor*iso*quinoline,** m.p. 89°, from oxy-*iso*carbostyril with $POCl_3$ together with **α-chloro-γ-hydroxy*iso*quinoline,** m.p. 196° (B. **33,** 986).

α-Chloro-β-methyl and **α-Chloro-β-phenyl *iso*quinolines,** melting at 36° and 77°, are obtained from the corresponding *iso*carbostyrils. The latter combines with aniline to

α-Anilino-β-phenyl *iso*quinoline, $C_9H_5(NHC_6H_5)N$, melts at 126° (B. **25,** 2709).

*Oxy*iso*quinolines,* iso*carbostyrils,* are isomeric with the carbostyrils (below). They result from the action of ammonia upon *iso*-coumarins. Another universal method of producing the *iso*carbostyrils consists in rearranging the reaction products of acid anhydrides and *o*-cyanobenzyl cyanide with alkalies:



$$C_6H_4\begin{cases}CH_2(CN)\\CN\end{cases} \xrightarrow{(CH_3CO)_2O} C_6H_4\begin{cases}C(CN)=C.CH_3\\ \qquad\qquad\;|\\ CN\qquad O.COCH_3\end{cases} \longrightarrow C_6H_4\begin{cases}C(CN)=C.CH_3\\ \qquad\qquad\;|\\ CO\text{——}NH\end{cases}$$

o-Cyanobenzyl Cyanide. ψ-Diacetyl-*o*-cyanobenzyl Cyanide. γ-Cyano-β-methyl *iso*carbostyril.

The alkyl cyan*iso*carbostyrils produced in this way are readily decomposed by concentrated sulphuric acid. The cyanogen group is eliminated, and β-alkyl *iso*carbostyrils result (B. **27,** 827, 2232; **29,** 2543).

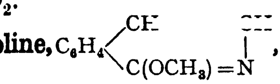
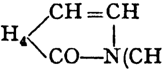
For producing αγ-dihydroxy*iso*quinolines or γ-hydroxy*iso*carbostyrils there is a method consisting in the transposition of phthalimido-aliphatic esters by means of Na alcoholate (B. **33,** 980; **38,** 3542):

$$C_6H_4\begin{cases}CO\\CO\end{cases}NCH_2CO_2R \cdot$$

The resulting hydroxy*iso*carbostyril carboxylic esters are easily transformed into oxy*iso*carbostyrils, which on reduction immediately yield *iso*carbostyrils.

*iso*Carbostyrils, like the carbostyrils, yield ethers of the hydroxyl and keto-forms. The latter are obtained from *iso*carbostyrils and alkyl iodides, while the former are mostly made through the interaction of α-chlor*iso*quinolines and sodium alcoholates.

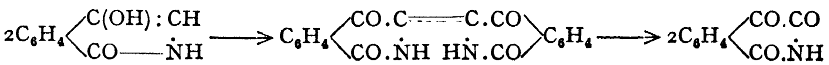
***iso*Carbostyril, *α-iso*Quinolone,** C_9H_7ON, results from *iso*coumarin and ammonia, and from ***iso*carbostyrilcarboxylic acid,** $C_9H_6ON.COOH$, a reaction product of ammonia and *iso*coumarin carboxylic acid, by the elimination of CO_2.

***α*-Methoxy*iso*quinoline,**  $C_6H_4\left<\begin{matrix}CH=CH\\ |\\ C(OCH_3)=N\end{matrix}\right.$, boiling at 240°, is produced by the interaction of the silver salt of *iso*carbostyril and methyl iodide. The isomeric ***N*-Methyl-*α-iso*quinolone,**  $C_6H_4\left<\begin{matrix}CH=CH\\ |\\ CO-N(CH_3)\end{matrix}\right.$, melting at 54° (40°) (B. **26,** R. 270; **27,** 205), is obtained from *iso*carbostyril, methyl iodide, and alkalies (B. **26,** R. 236), or by the action of alkaline potassium ferricyanide upon methyl *iso*quinolinium iodide; other *N*-alkyl *iso*quinolones are produced by the action of primary amines upon *iso*coumarin (B. **27,** 198) or its carboxylic acid. ***β*-Methyl*iso*carbostyril,** $C_9(CH_3)H_6ON$, melts at 211°; ***β*-ethyl*iso*carbostyril** melts at 141°; ***β-iso*propyl*iso*carbostyril** melts at 221° (B. **29,** 2393). ***β*-Phenyl*iso*carbostyril,** *isobenzal phthalimidine,* melting at 197°, also results from the action of ammonia upon *iso*benzalphthalide (B. **18,** 2448; **27,** 2237).

A *bz*-2, 3, 4-**Trihydroxy-*γ*-methyl*iso*carbostyril,** $C_6H(OH)_3$:-$[C_3H_2(CH_3)ON]$, is derived from the corresponding *iso*coumarin derivative, which is produced when concentrated sulphuric acid acts upon gallacetol, $C_6H_2(OH)_3.CO.O.CH_2.COCH_3$ (B. **26,** 419).

***iso*Carbostyril-*β*-carboxylic acid,** m.p. 319° with dec., has been isolated from fasciated plants of *Syndesmon Thallictroides* in the form of its methyl ester (C. 1909, I. 87).

***γ*-Hydroxy*iso*carbostyril,** $C_9H_7O_2N$, is isomeric with homo-phthalimide. It is formed on the saponification of ***γ*-hydroxy*iso*carbostyril-*β*-carboxylic ester,** $C_9H_6O_2N(CO_2C_2H_5)$, m.p. 222°, the transposition product of phthalylglycine ester, $C_6H_4(CO)_2NCH_2CO_2C_2H_5$. The hydroxy*iso*carbostyril, on reduction with HI, gives *iso*carbostyril. Oxidation easily transforms it, like indoxyl, into indigo, a ring homologue of indigo, the so-called **carbindigo,** a vermilion-coloured powder. As indigo is oxidized to isatin, so carbindigo is converted by fuming nitric acid into phthalonimide, which is also formed from hydroxy*iso*carbostyril direct, by oxidation with fuming nitric acid:



$$2C_6H_4\left<\begin{matrix}C(OH):CH\\ CO-NH\end{matrix}\right. \longrightarrow C_6H_4\left<\begin{matrix}CO.C=C.CO\\ CO.NH\quad HN.CO\end{matrix}\right>C_6H_4 \longrightarrow 2C_6H_4\left<\begin{matrix}CO.CO\\ CO.NH\end{matrix}\right.$$

With sodium methylate and methyl iodide, hydroxy-*iso*-carbostyril gives *γ*-methoxy*iso*carbostyril, m.p. 171°. With benzaldehyde and with phthalic acid anhydride it condenses with loss of water. With phthalonimide (see above) it gives carbindigo (B. **35,** 2421).

***β*-Methyl-, *β*-ethyl-,** and ***β*-phenyl-*γ*-hydroxy*iso*carbostyril** are obtained from phthalimido-propionic acid ester, -butyric acid ester, and -phenylacetic ester by transposition and splitting (B. **37,** 1685, 1791).

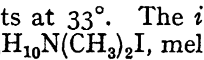
HYDRO-*ISO*-QUINOLINES.

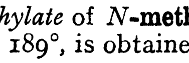
(1) *Dihydro*iso*quinolines* are formed synthetically from acylated ω-phenyl ethylamines by means of P_2O_5 (B. **42,** 1973), and by the action of alkyl magnesium haloids upon the iodalkylates of *iso*quinoline (B. **42,** 1750). In the former case, Δ^{α}-dihydro*iso*quinolines are formed, and in the latter case, Δ^{β}-dihydro*iso*quinolines. These may be partly oxidized by means of $KMnO_4$ in acid solution to the corresponding *iso*quinolines.

α-Methyldihydro*iso*quinoline, $C_9H_8(CH_3)N$, b.p. 236°, **α-Phenyldihydro*iso*quinoline,** $C_9H_8(C_6H_5)N$, m.p. 73°, **α-Benzyldihydro*iso*quinoline,** $C_9H_8(CH_2C_6H_5)N$, b.p.$_{12}$ 196°. **2,3-Methylenedioxydihydro*iso*quinoline,** $(CH_2O_2)C_6H_2(C_3H_5N)$, m.p. 91°, from formyl homopiperonylamine with P_2O_5; with CH_3I it yields *hydrastinine hydriodide* (C. 1911, II. 112). ***N*,α-Dimethyldihydro*iso*quinoline,** $C_9H_7(CH_3)NCH_3$, b.p.$_{20}$ 150°, and ***N*-Methyl-α-benzyldihydro*iso*quinoline,** $C_9H_7(CH_2C_6H_5)NCH_3$, b.p.$_9$ 170°–180°, from *iso*quinoline iodo-methylate with CH_3MgI and $C_6H_5CH_2MgCl$ respectively.

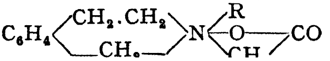
The *iso*carbostyrils are *ketodihydro*iso*quinolines.*

(2) *Tetrahydro*iso*quinolines* have been produced synthetically by the condensation of ω-phenyl ethylamines with aldehydes (B. **44,** 2030); or when *iso*quinoline is reduced with tin and hydrochloric acid, or, better, with sodium and alcohol. Tetrahydro*iso*quinoline shows the properties of the alkylic benzylamines, while tetrahydroquinoline manifests those of an alkylic aniline:

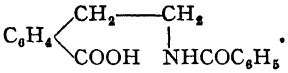

Tetrahydroquinoline.


Tetrahydro*iso*quinoline.

Tetrahydro*iso*quinoline, $C_9H_{11}N$, boiling at 233°, obtained from ω-phenylethylamine, methylal and conc. HCl, or by the reduction of *iso*quinoline, is a powerful base, which absorbs carbon dioxide from the air and reduces warm ammoniacal silver solutions. Its *nitroso-compound* melts at 33°. The *iodomethylate* of ***N*-methyl tetrahydro*iso*quinoline,** $C_9H_{10}N(CH_3)_2I$, melting at 189°, is obtained from methyl iodide and tetrahydro*iso*quinoline.

The *N*-methyltetrahydro*iso*quinoline itself, b.p. 212°, is best obtained by the reduction of *iso*quinoline iodomethylate with Cu and HCl. Chromic acid oxidizes it to *phthalone-methylimide* (B. **37,** 1943); while *N*-ethyl and *N*-propyl tetrahydro*iso*quinolines, with iodo-acetic acid *l*-menthyl ester, each yield two stereo-isomeric addition products, $C_9H_{10}N(R)(CH_2CO_2C_{10}H_{19})I$, of different optical rotations. From these, by the action of moist silver oxide, menthol may be split off, and two pairs of opposite optically active betaïnes of the formula  are produced. Here we have, therefore, a *synthesis* of optically active nitrogen compounds (B. **41,** 456; **42,** 2138).

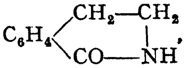
***N*-Benzoyltetrahydro*iso*quinoline,** boiling at 245° to 250° (50 mm.), is converted by $KMnO_4$ into ω-benzoylaminoethyl-*o*-benzoic acid,



$$C_6H_4\left\langle\begin{matrix}CH_2—CH_2\\ COOH \quad NHCOC_6H_5\end{matrix}\right.$$

. The latter readily parts with water and becomes the benzoyl derivative of—

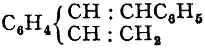
Hydro*iso*carbostyril, *ketotetrahydro*iso*quinoline,*



$$C_6H_4\left\langle\begin{matrix}CH_2—CH_2\\ CO—NH\end{matrix}\right.$$

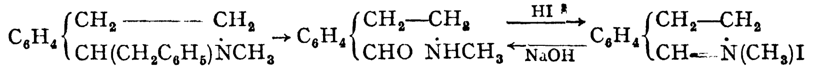
, melting at 71° (B. **26,** 1220).

***N*,*a*-Dimethyltetrahydro*iso*quinoline,** $C_9H_9(CH_3)NCH_3$, b.p.$_{20}$ 126°; ***N*-Methyl-*a*-benzyltetrahydro*iso*quinoline,** $C_9H_9(CH_2C_6H_5)NCH_3$, b.p.$_{12}$ 178°, is the foundation substance of Laudanosine; it can be split up by A. W. Hofmann's method to *o*-vinylstilbene,



$$C_6H_4\left\{\begin{matrix}CH:CHC_6H_5\\ CH:CH_2\end{matrix}\right.$$

(B. **42,** 1750). Oxidized with manganese dioxide and dilute H_2SO_4, it splits off the benzyl group in the form of benzaldehyde, and yields *ω*-methylamino-*o*-ethylbenzaldehyde, from which acids form *N*-methyldihydro*iso*quinolinium salts (C. 1910, I. 185):



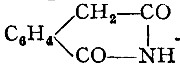
$$C_6H_4\left\{\begin{matrix}CH_2 — CH_2\\ CH(CH_2C_6H_5)NCH_3\end{matrix}\right. \rightarrow C_6H_4\left\{\begin{matrix}CH_2—CH_2\\ CHO \quad NHCH_3\end{matrix}\right. \underset{NaOH}{\overset{HI}{\rightleftarrows}} C_6H_4\left\{\begin{matrix}CH_2—CH_2\\ CH=N(CH_3)I\end{matrix}\right.$$

Compare the splitting up of benzyl*iso*quinoline iodomethylate and of the dihydropyridines (above).

2,3-**Dimethoxydihydro*iso*quinoline,** b.p.$_{24}$ 207°, is analogously formed from tetrahydropapaverine (C. 1909, II. 2178; 1910, I. 1258).

Tetrahydro*iso*quinoline-*β*-carboxylic acid, $C_9H_{10}(CO_2H)N$, m.p. 311°, is formed from phenylalanine, methylal, and concentrated HCl. It decomposes into CO_2 and tetrahydro*iso*quinoline (B. **44,** 2034).

The homo-phthalimides—*e.g.*,



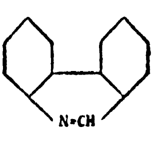
$$C_6H_4\left\langle\begin{matrix}CH_2—CO\\ CO—NH\end{matrix}\right.$$

—are *diketotetrahydro*iso*quinolines.*

The alkaloids *berberine, hydrastine, narcotine,* are derivatives of tetrahydro*iso*quinoline.

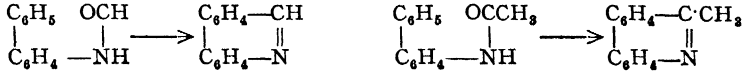
V. PHENANTHRIDINE.

It can be considered both as a benzo-derivative of quinoline and of *iso*quinoline. It results also from phenanthrene by replacing one of the intermediate —CH =groups by nitrogen:



It is isomeric with the naphtho-quinolines.

Phenanthridines are produced upon heating the acidyl derivatives of *o*-aminodiphenyl (B. **29,** 1182):

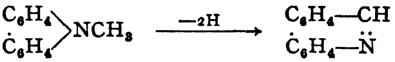


$$\begin{matrix}C_6H_5 & OCH\\ | & |\\ C_6H_4 & —NH\end{matrix} \longrightarrow \begin{matrix}C_6H_4—CH\\ | \quad\quad \|\\ C_6H_4—N\end{matrix} \qquad \begin{matrix}C_6H_5 & OCCH_3\\ | & |\\ C_6H_4 & —NH\end{matrix} \longrightarrow \begin{matrix}C_6H_4—C{\cdot}CH_3\\ | \quad\quad \|\\ C_6H_4—N\end{matrix}$$

Phenanthridine, $C_{13}H_9N$, melting at 104° and boiling above 360°, results by heating benzylidene aniline:

$$C_6H_5CH{=}NC_6H_5 \xrightarrow{-2H} \dot{C}_6H_4CH{=}N\dot{C}_6H_4$$

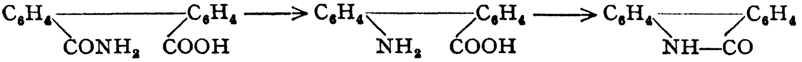
and from *N*-methylcarbazole, like pyridine from methylpyrrole and quinoline from *a*-methylindole (B. **38,** 1950):



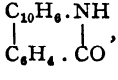
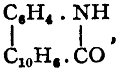
and when phenanthridone is distilled with zinc dust. Bleaching powder and cobalt nitrate reoxidize it to phenanthridone (B. **26,** 1964), while tin and hydrochloric acid reduce it to **dihydrophenanthridine,** $C_6H_4CH_2—NHC_6H_4$, melting at 90° (A. **266,** 142).

ms-**Methyl-, ethyl-,** and **phenyl-phenanthridine** melt at 85°, 55°, and 109° (B. **29,** 1184).

Phenanthridone, $C_6H_4CO.NHC_6H_4$, melting at 293°, is produced on treating diphenamic acid with bromine and caustic potash:



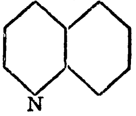
as well as by the rearrangement of *o*-aminophenylene ketone, on fusion with caustic potash; by transposition of diphenylene ketone oxime with zinc chloride; and, finally, from *o*-diphenyl urethane, $C_6H_5C_6H_4$-$NHCO_2C_2H_5$, on digesting it with zinc chloride (B. **26,** R. 712; **28,** R. 455; **29,** 230, 1188). Phenanthridone and phosphorus pentachloride yield *chlorophenanthridine*, $C_6H_4CCl{=}NC_6H_4$, melting at 116°. *N*-**Methyl phenanthridone,** $C_{13}H_8ONCH_3$, melting at 108°, is formed in the action of alkaline potassium ferricyanide upon *methyl phenanthridinium iodide*, $C_{13}H_9N.ICH_3$ (B. **26,** 1962; compare pyridinium and quinolinium compounds, pp. 164, 192). A by-product is *N*-**methyldihydrophenanthridine,** $C_{13}H_{20}NCH_3$ (B. **35,** 2534).

a-**Naphtho-phenanthridone,**  $\begin{array}{l}C_{10}H_6.NH\\ |\quad\quad\ |\\ C_6H_4.CO\end{array}$, m.p. 33°, and *β*-**Naphtho-phenanthridone,**  $\begin{array}{l}C_6H_4.NH\\ |\quad\quad\ |\\ C_{10}H_6.CO\end{array}$, m.p. 338°, from *a*- and *β*-chryso-diphenaminic acids respectively, on distillation with zinc dust yield *a*- and *β*-naphtho-phenanthridines, m.p. 135° and 182° respectively (A. **335,** 124).

VI. NAPHTHYRIDINES, NAPHTHINOLINES.

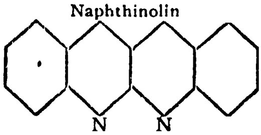
The union of two pyridine nuclei or of two quinoline nuclei in the manner of naphthalene gives rise to the hypothetical parent substances:

Naphthyridin



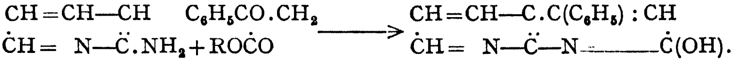
and

Naphthinolin



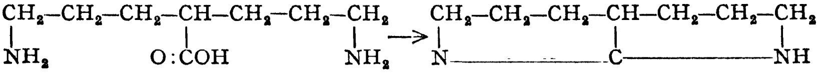
Thus far only the following derivatives of these bodies have been prepared:

α-**Hydroxy-γ-phenyl-naphthyridine**, m.p. 150°, by the condensation of α-amino-pyridine with benzoyl acetic ester (C. 1911, I. 987):

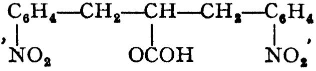


$$\begin{array}{l} CH{=}CH{-}CH \quad C_6H_5CO.CH_2 \\ \dot{C}H{=}\ N{-}\ddot{C}.NH_2+RO\dot{C}O \end{array} \longrightarrow \begin{array}{l} CH{=}CH{-}C.C(C_6H_5):CH \\ \dot{C}H{=}\ N{-}\ddot{C}{-}N{-\!-\!-\!-}\dot{C}(OH). \end{array}$$

Octohydronaphthyridine, $C_8H_{14}N_2$ (forms a *platinum double salt*), melts at 227°, and is prepared from γ,γ-diaminodipropyl acetic acid (B. **26,** 2137):



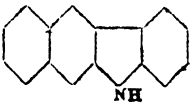
$$\begin{array}{l} CH_2{-}CH_2{-}CH_2{-}CH{-}CH_2{-}CH_2{-}CH_2 \\ | \qquad\qquad\quad | \qquad\qquad\quad | \\ NH_2 \qquad\ O{:}COH \qquad NH_2 \end{array} \longrightarrow \begin{array}{l} CH_2{-}CH_2{-}CH_2{-}CH{-}CH_2{-}CH_2{-}CH_2 \\ | \qquad\qquad\quad | \qquad\qquad\quad | \\ N{-\!-\!-\!-\!-}C{-\!-\!-\!-\!-}NH \end{array}$$



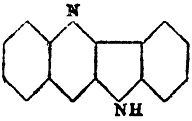
Tetrahydronaphthinoline, $C_{16}H_{14}N_2$, melting at 212°, is formed by the reduction of *o*-dinitrodibenzylacetic acid, $\begin{array}{l} C_6H_4{-}CH_2{-}CH{-}CH_2{-}C_6H_4 \\ | \qquad\qquad\ \ | \qquad\qquad | \\ NO_2 \qquad OCOH \qquad NO_2 \end{array}$, in a manner similar to that of the naphthyridine body. Mercury acetate oxidizes it very easily to *dihydronaphthinoline*, $C_{16}H_{12}N_2$, melting at 201°, the salts of which show an intense green fluorescence. It is reduced by sodium amalgam in glacial acetic acid solution to *hexahydronaphthinoline*, $C_{16}H_{16}N_2(+1\frac{1}{2}H_2O)$, melting at 128° (B. **27,** 2244).

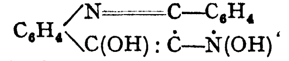
VII. QUINDOLINES.

These are formed by the junction of a quinoline and an indole nucleus. Two isomeric quindolines are known, which may be distinguished as *peri-* (I.) and *ana*-quindoline (II.) respectively:



II.

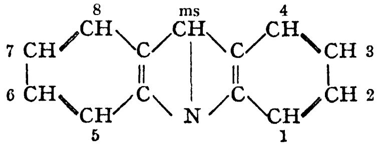


peri-**Quindoline,** m.p. 343°, is formed by the reduction of *oo*-dinitrocyano-dibenzyl, $NO_2C_6H_4CH_2CH(CN)C_6H_4NO_2$, with alcohol ammonium sulphide (B. **30,** 3020). The isomeric *ana*-**quindoline,** m.p. 248°, is obtained by the condensation of indoxyl and indoxylic acid respectively with *o*-amino-benzaldehyde, as well as by the reduction of dihydroxy-quindoline,  $C_6H_4{<}\begin{matrix}N{=\!=\!=}C{-}C_6H_4\\ C(OH):\dot{C}{-}\dot{N}(OH)\end{matrix}$, by means of HI and phosphorus. The latter is formed by the action of caustic soda upon *oo'*-dinitro-benzyl malonic ester.

ana-**Quindoline carboxylic acid,** $C_{15}H_9N_2CO_2H$, is formed by the condensation of indoxyl with isatinic acid in alkaline solution. Also by intermediate formation of these components on heating indigo with sodium hydro-sulphite and alkali (B. **43,** 3489, 3512).

VIII. ACRIDINE GROUP.

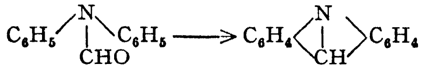
Acridine represents an anthracene, one of the intermediate CH-groups of which is replaced by nitrogen:



Its relations to quinoline and pyridine follow from its oxidation to quinoline dicarboxylic acid and pyridine tetracarboxylic acids.

Acridine occurs in the crude anthracene of coal-tar. Some of its derivatives are important technically as dyes. Acridines may be synthesized:

1. From diphenylamine with carboxylic acids, or from the acidyl derivatives of diphenylamine, if they be heated together with zinc chloride. This is analogous to the formation of the phenanthridines from acidyl *o*-amino-diphenyls (Bernthsen, A. **224,** 1):

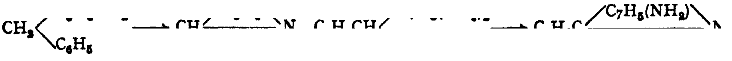


Formyldiphenylamine. Acridine.

This reaction is regarded as a proof of the para-union in acridine.

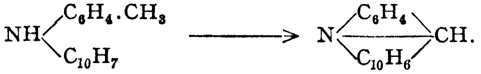
Homologous acridines are similarly obtained from diphenylamine and the higher fatty acids. In them the hydrogen of the CH-group is replaced by alkyls. They are called *meso*-derivatives (B. **18,** 690; **25,** R. 940). The substituted diphenylamines (B. **24,** 2039), ditolylamine, phenylnaphthylamine, etc., react just like diphenylamine.

2. Various acridine compounds have been prepared from the *o*-amino-derivatives of di- and tri-phenyl methane (B. **26,** 3085):



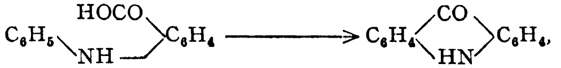
and naphthacridines are also obtained by the condensation of aldehydes with anilines and naphthols, and of *o*-aminobenzyl alcohol, or *o*-aminobenzyl chloride with naphthols or naphthylamine (B. **36,** 1027; **38,** 3787; **39,** 2623; C. 1908, I. 384).

3. Naphthacridines are also obtained from *o*-tolyl-naphthylamines by oxidation with S or PbO (B. **37,** 2923; compare C. 1906, I. 58):



$$NH\langle^{C_6H_4.CH_3}_{C_{10}H_7} \longrightarrow N\langle^{C_6H_4}_{C_{10}H_6}\rangle CH.$$

4. Acridones are prepared from the arylanthranilic acids (B. **26,** R. 712; **27,** R. 642), just as anthraquinone is obtained from benzoyl benzoic acid:

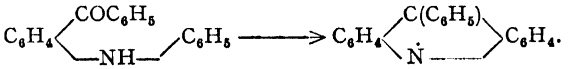


$$C_6H_5\langle^{HOCO}_{NH}\rangle C_6H_4 \longrightarrow C_6H_4\langle^{CO}_{HN}\rangle C_6H_4,$$

Phenylanthranilic Acid. Acridone.

or by the action of phenols (naphthols, etc.) upon acetanthranilic acid (B. **25,** 1983, 2740).

Similarly, *ms*-phenylacridines are formed by eliminating water from *o*-anilinobenzophenones with concentrated H_2SO_4 (B. **39,** 298, 356):



$$C_6H_4\langle^{COC_6H_5}_{NH}\rangle C_6H_5 \longrightarrow C_6H_4\langle^{C(C_6H_5)}_{N}\rangle C_6H_4.$$

The acridines are very stable compounds. They are more feeble bases than the pyridines and quinolines. They combine with alkyl iodides to alkyl acridinium iodides, which are converted by alkaline potassium ferricyanide (similar to the pyridinium, quinolinium, and *iso*-quinolinium iodides) into *n*-alkyl acridones. When the acridines are reduced they become dihydro-acridines, which readily revert to the acridines.

Acridine, $C_{13}H_9N$, melts at 110°. It sublimes at 100°. Its solutions have a blue fluorescence. It is isomeric with phenanthridine and the naphtho-quinolines. In addition to the general reactions, it is also produced when diphenylamine is heated with chloroform and zinc chloride to 200° (B. **17,** 101), and in the distillation of acridone with zinc dust (B. **26,** R. 714). Potassium permanganate oxidizes it to *acridic acid,* or quinoline-α,β-dicarboxylic acid, from which it was concluded that quinoline and pyridine had the diagonal formula (Riedel, B. **16,** 1612).

In the oxidation of the acridinium compounds the heterocyclic nucleus is ruptured and phenylaminobenzoic acid, $C_6H_5.NH.C_6H_4.COOH$, is produced.

Acridine, in chloroform or CS_2 solution, forms with halogens certain loose addition products of the formula $C_{13}H_9N(Hlg)_2$, which regenerate acridine under the action of water, or even on standing, with evolution of the halogen. The dichloride melts at 240°, the dibromide at 187°, the di-iodide at 145° (C. 1904, II. 1059).

Pheno-1,2-naphthacridine, $C_6H_4\left\{\begin{matrix}CH[\alpha]\\ |\\ N\ \ [\beta]\end{matrix}\right\}C_{10}H_6$, m.p. 131°, from formaldehyde, aniline, and β-naphthol, or from *o*-aminobenzyl alcohol or *o*-aminobenzyl chloride with *β*-naphthol (B. **35,** 2670; **37,** 3078); and from *o*-tolyl-*β*-naphthylamine by oxidation with PbO.

Pheno-2,1-naphthacridine, $C_6H_4\left\{\begin{matrix}CH[\beta] \\ | \\ N\ [\alpha]\end{matrix}\right\}C_{10}H_6$, m.p. 108°, by the oxidation of *o*-tolyl-*α*-naphthylamine with PbO (B. **37,** 2922). We may note the formation of pheno-1,2- and -2,1-naphthacridine in the pyrogenic way from benzylidene-*β*- and -*α*-naphthylamine respectively, $C_6H_5CH:NC_{10}H_7$, while benzylideneaniline, under similar conditions, does not yield acridine, but phenanthridine.

Of the six theoretically possible dinaphthacridines, four have been prepared (C. 1906, II. 1505).

1,2-2′,1′-**Dinaphthacridine,** $C_{10}H$ ${}_0H_6$, m.p. 228°, and

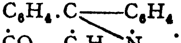
1,2-1′,2′-**Dinaphthacridine,** $C_{10}H_6\left\{\begin{matrix}[\beta \\ \cdot \\ [\alpha]\dot{C}H[\alpha]\end{matrix}\right\}C_{10}H_6$, m.p. 216°, from trioxymethylene and *β*-naphthol with *α*- and *β*-naphthylamine respectively (B. **36,** 1027).

2,1-2′,1′-**Dinaphthacridine,** $C_{10}H_6\left\{\begin{matrix}[\alpha]N\ [\alpha] \\ \cdot \\ [\beta]\dot{C}H[\beta]\end{matrix}\right\}C_{10}H_6$, m.p. 185°, from methylene chloride and *α*-naphthylamine. The fourth isomeride, 1,2-2′,3′-**dinaphthacridine,** $C_{10}H_6\left\{\begin{matrix}[\beta]N\ [\beta] \\ \cdot \\ [\alpha]\dot{C}H[\beta]\end{matrix}\right\}C_{10}H_6$, m.p. 203°, has been prepared from the corresponding dinaphthacridone by zinc dust distillation (B. **34,** 4146; see also B. **35,** 4164).

Diphenanthacridine, from methylene chloride and 9-amino-phenanthrene (C. 1908, II. 2013).

ms-**Methylacridine,** $C_{13}H_8(CH_3)N$, m.p. 114°, from acetyldiphenylamine, like quinaldine and picoline, forms condensation products with benzaldehyde and chloral: $C_{13}H_8NCH_2CH(OH)C_6H_5$, m.p. 197° (B. **38,** 2840), and $C_{13}H_8NCH_2CH(OH)CCl_3$; the latter, with alkalies, yields ms-*acridyl-acrylic acid,* $C_{13}H_8NCH:CHCOOH$; $KMnO_4$ oxidizes this to acridyl aldehyde, $C_{13}H_8NCHO$, and further to ms-*acridine carboxylic acid,* $C_{13}H_8NCOOH$ (B. **20,** 1541). *ms*-**Benzylacridine,** $C_{13}H_8(CH_2$-$C_6H_5)N$, m.p. 173°, from diphenylamine with phenyl acetic acid and $ZnCl_2$ at 200° (B. **37,** 1565).

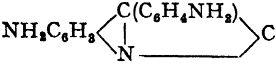
ms-**Phenylacridine,** $C_{13}H_8(C_6H_5)N$, m.p. 181°, from diphenylamine and benzoic acid, crystallizes from benzene, together with benzene of crystallization. *p*-**Dimethylamino-*ms*-phenylacridine,** $(C_{13}H_8N)C_6H_4N(CH_3)_2$, m.p. 279°, by the condensation of acridone and dimethyl-aniline by means of $POCl_3$ (B. **40,** 4795). **Hydroxy-*ms*-phenylacridine** (see C. 1904, II. 1509). *ms*-**Acridyl-benzoic acid,** $N(C_6H_4)_2$-CC_6H_4COOH, m.p. 347°, is prepared from diphenyl-amine and phthalic acid; by heating with methyl iodide, it is converted into the HI salt of its methyl ester, m.p. 173° (B. **37,** 1007). Treatment with fuming sulphuric acid condenses it to a compound containing a combined acridine and anthraquinone nucleus,



$\begin{matrix}C_6H_4.C & \text{---} & C_6H_4 \\ \dot{C}O & \text{---} \dot{C}_6H_3 . & \dot{N}\end{matrix}$

. This compound is also formed from *α*-anilido-anthraquinone, and closely approaches the cœroxenes in its structure and behaviour (C. 1902, II. 368; A. **348,** 242).

Chrysaniline, *ms-p*-**Aminophenyl-2-aminoacridine,**



$NH_2C_6H_3{<}\overset{C(C_6H_4NH_2)}{\underset{N}{|}}{>}C_6H_4$, melting at 268°, is the chief constituent of the beautiful yellow dye *phosphin,* which is obtained as a by-product in the rosaniline manufacture. It forms red-coloured salts; these dye silk and wool a beautiful yellow. Their solutions exhibit a beautiul yellow-green fluorescence.

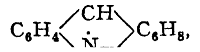
The formation of chrysaniline from pararosaniline proceeds evidently according to the diagram of method 2 for the acridines.

Yellow to orange-red dyestuffs are also provided by a series of other amino-derivatives of acridine, *ms*-phenylacridine, and the corresponding alkylacridinium salts (B. **34,** 4307)—*e.g., Acridine Yellow,* 2,7-**dimethyl**-3,6-**diamino-acridine,** obtained from tetramino-ditolyl methane by heating with HCl and oxidation with ferric chloride; **Benzo-flavine,** ms-*phenyldiamino-2,7-dimethylacridine,* m.p. 231°, obtained from benzaldehyde and *m*-toluylene diamine (B. **32,** 2352).

Hydro-acridines.—*ms*-**Dihydroacridine,** $NH(C_6H_4)_2CH_2$, is formed when acridine is reduced with zinc dust and hydrochloric acid. It *no longer* manifests basic properties, and melts at 168°. It reduces ammoniacal silver nitrate with the regeneration of acridine. It has been found in coal-tar (B. **42,** 1178). *N*-**Methyl-** and *N*-**phenyldihydroacridine,** m.p. 96° and 119°, by reduction of the corresponding acridones (B. **39,** 2720; **40,** 2515). Numerous alkylated *ms*-dihydroacridines have been obtained by transposition of acridin iodalkylates with alkyl magnesium haloids: *N*-**Methyl**-*ms*-**methyl-, -ethyl-, -benzyl-,** and **-phenyl-dihydroacridine,** $CH_3N(C_6H_4)_2CHR$, m.p. 138°, 72°, 108°, and 104°; on oxidation with iodine solution these dihydroacridines pass into the iodo-methylates of the *ms*-alkylacridines, which can be again transformed with alkyl-magnesium haloids (B. **42,** 1746).

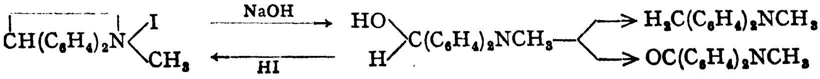
Bz-*tetrahydroacridines* have been obtained by the application of quinoline syntheses 2 and 4*c* (above) to the cyclic ketones of the hexamethylene series: (1) By the condensation of cyclo-hexanones with aromatic *o*-amino-aldehydes and -ketones; (2) by the condensation of *a*-acylated *cyclo*-hexanones with aniline and its homologues (A. **377,** 70).

Bz-**Tetrahydroacridine,**

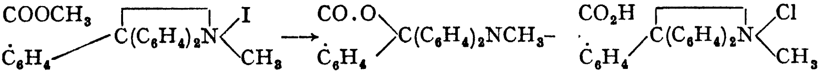


$C_6H_4{<}\overset{CH}{\underset{N}{\cdot}}{>}C_6H_8$, m.p. 55°, on distillation over lead oxide, yields acridine.

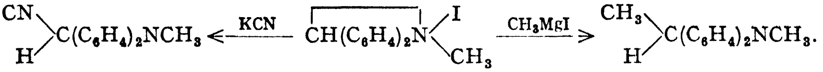
Alkyl-acridinium Compounds.—**Acridine iodo-methylate,** $C_{13}H_9N(CH_3I)$, resembles, in its transformations, the iodalkylates of pyridine, quinoline, and *iso*quinoline; with NaHO the transposition of the unstable acridinium base produces *N*-**methyldihydroacridol** (B. **37,** 576), which, with acids, regenerates to acridinium salts. It is transformed by alkaline potassium ferricyanide solution into *N*-methylacridone, and on heating with NaHO alone is transformed into a mixture of *N*-methyldihydroacridine and *N*-methylacridone (B. **35,** 2534):



Similarly, *ms*-phenylacridine iodomethylate produces *N*-**methyl-*ms*-phenyl-hydracridol,** $\genfrac{}{}{0pt}{}{C_6H_5}{HO}{>}C(C_6H_4)_2NCH_3$, which is also obtained by the union of *N*-methylacridone with phenyl magnesium bromide, and which also regenerates the acridinium salts with acids (B. **37,** 575). From *ms*-benzylacridine iodomethylate, instead of hydracridol, we obtain *N*-**methyl-*ms*-benzylidenehydracridine,** $C_6H_5CH:C(C_6H_4)_2NCH_3$, m.p. 141°, which is easily split up into benzaldehyde and *N*-methyl acridone (B. **37,** 1564). We may note the behaviour of *ms*-acridyl benzoic acid ester, the iodo-methylate of which, treated with NaHO, yields *N*-**methyl-hydracridolbenzoic acid lactone,** m.p. 245°. This body, with HCl, gives the chloro-methylate of acridyl benzoic acid (B. **37,** 1002):

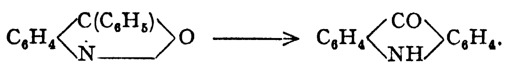


With alkyl magnesium haloids the acridine iodalkylates give alkylated *ms*-dihydro-acridines, and with potassium cyanide *N*-**alkyl-*ms*-cyanodihydroacridines** (B. **42,** 1746; **44,** 2052):



Acridone, *ketodihydroacridine,* $C_6H_4{<}\genfrac{}{}{0pt}{}{CO}{NH}{>}C_6H_4$, melting at 354°, can be distilled. It is formed when sulphuric acid at 100° acts upon phenylanthranilic acid, and by the dry distillation of the anilide of salicyclic acid, when it may be assumed that the latter first rearranges itself to phenylanthranilic acid. The salicyltoluides also yield methylated acridones (B. **29,** 1189).

We may also note the formation of acridone by the transposition of *C*-phenyl-anthranil on heating alone or on simultaneous treatment with concentrated sulphuric and nitric acids (B. **42,** 592, 1716):



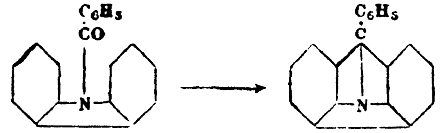
Compare the transformation of *C*-methyl-anthranil into indoxyl. With methyl iodide and alkali acridone gives *N*-**methyl-acridone,** $CO(C_6H_4)_2NCH_3$, m.p. 203°, the formation of which, from the iodomethylate of acridine, has already been mentioned. Phosphorus sulphide produces **thio-acridine,** $CS(C_6H_4)_2NH$ or $HS.C(C_6H_4)_2N$, m.p. 275°. This has also been obtained by heating acridine with sulphur. It has an acid character, and is alkylated on the sulphur on treating with alkali and halogen alkyl, giving **acridyl methyl sulphide,** $N(C_6H_4)_2CSCH_3$, m.p. 114°. With PCl_5 acridone, like thio-acridone, gives *ms*-**chloracridine,** $N(C_6H_4)_2CCl$, m.p. 119°; *ms*-**bromacridine,** m.p. 116°, from thio-acridone with phosphorus bromide; *ms*-**iodacridine,** m.p. 169°, from bromacridine with NaI (J. pr. Ch. [2], **64,** 471). On heating *N*-methyl acridone with PCl_5 we obtain *ms*-**chloracridinium chloromethylate,** $C_{13}H_8ClN(CH_3.Cl)$, m.p. 73°, which, with aniline, becomes *ms*-anilino-acridinium chloro-methylate; the ammonium base corresponding to the latter splits off H_2O and gives **N-methylacridone anil,** $C_6H_5N:C(C_6H_4)_2NCH_3$, m.p. 163° (B. **32,** 1309). On heating with zinc dust acridone forms acridine, and with Na and alcohol dihydro-acridine. On the reduction of N-methylacridone, see B. **42,** 1176. **N-Phenylacridone,** $CO(C_6H_4)_2NC_6H_5$, m.p. 276°, from diphenyl anthranilic acid and concentrated H_2SO_4 (B. **40,** 2450).

The following are obtained in the same way as acridone:

4-Methylacridone, $CH_3.C_6H_3.\left(^{CO}_{NH}\right)C_6H_4$, melting at 346°;
2-Methylacridone, melting at 338°;
2,4-Dimethylacridone, melting at 297° (B. **27,** R. 642);
Pheno-naphthacridone, $C_6H_4<^{CO}_{NH}>C_{10}H_6$; and
Dinaphthacridone, $C_{10}H_6<^{CO}_{NH}>C_{10}H_6$ (B. **25,** 2744).
Anthacridone (see A. **380,** 336).

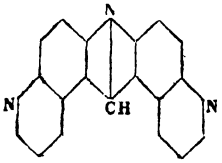
***Bz*-Tetrahydro-acridone,** $C_6H_4<^{CO}_{NH}>C_6H_8$, m.p. 358°, by the condensation of *cyclo*hexanone with anthranilic acid (B. **42,** 621). **Decahydro-acridinedione,** $CH_2(C_6H_6O)_2NH$, from methylene *bis*-dihydro-resorcin with alcoholic NH_3, gives acridine on heating with zinc dust, and on oxidation with N_2O_3 it gives **octo-hydro-acridinedione,** m.p. 141° (A. **309,** 353).

Peculiar acridine derivatives are obtained by the condensation of acidyl carbazoles (B. **24,** R. 829; **25,** R. 114):

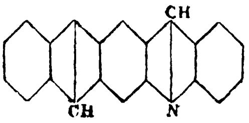


Benzoyl-carbazole. *ms*-Phenyl-carbazacridine, m.p. 186°.

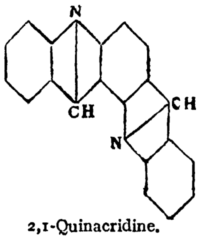
By the linking of the acridine nucleus with one or two pyridine or quinoline nuclei, compounds are obtained which may be termed pyracridines and quinacridines respectively:



Dipyracridine.



3,2-Quinacridine.

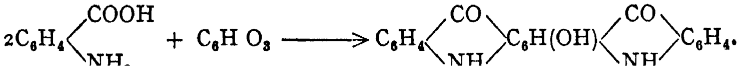


2,1-Quinacridine.

Dipyracridine, m.p. 303°, is obtained by the condensation of methylene chloride with 3-amino-quinoline; α- and **β-naptho-pyracridine,** m.p. 268° and 220°, from methylene chloride with 3-amino-quinoline and α- and β-naphthol respectively (see acridine synthesis 2 and C. 1909, II. 2177).

3,2-**Quinacridine,** yellow needles, m.p. 245°, is formed from 3,2-**quinacridone,** $C_6H_4<_{CO}^{NH}>C_6H_2<_{NH}^{CO}>C_6H_4$, which occurs in yellow needles melting at 394°, and is obtained synthetically from *p*-phenylene dianthranilic acid with concentrated H_2SO_4. This latter body is first reduced to **dihydro-quinacridine,** red needles, m.p. 243°, by means of Na and alcohol, and then oxidized with $FeCl_3$ and nitric acid. The quinacridone, when oxidized with PbO_2 in benzene in the presence of glacial acetic acid, loses two H atoms and yields the quinone-like substance **dehydro-quinacridone,** $C_6H_4<_{CO}^{N}>C_6H_2<_{N}^{CO}>C_6H_4$. This forms blue-black flakes soluble in benzene with a blue coloration, and possesses remarkable oxidizing properties (B. **39,** 1693; **40,** 2522; **43,** 2209).

The isomeric 2,1-**quinacridine,** m.p. 213°, is obtained by zinc dust distillation from hydroxy-quinacridine, which itself is produced by heating phloroglucin with anthranilic acid:

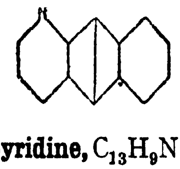


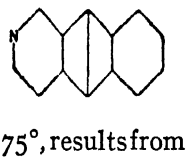
$$2C_6H_4<_{NH_2}^{COOH} + C_6H\,O_3 \longrightarrow C_6H_4<_{NH}^{CO}>C_6H(OH)<_{NH}^{CO}>C_6H_4.$$

In a similar manner, phloroglucin condenses with *o*-amino-benzaldehyde to form **oxy-quinacridine,** garnet-black needles, m.p. 360°. Simultaneously the junction of 1 molecule phloroglucin with 3 molecules *o*-amino-benzaldehyde produces the so-called **phloroquinyl** or 2,1-4,3-*diquinacridine,* $C_6\left(<_{\dot{C}H}^{N}>C_6H_4\right)_3$, yellowish-brown needles, m.p. 403°, a ring homologue of *phenotripyridine* (B. **29,** 76; **39,** 385). Concerning *diacridines,* see B. **39,** 2650.

IX. ANTHRAPYRIDINES.

The *α*- and *β*-anthrapyridines are isomeric with acridine:





α-**Anthrapyridine,** $C_{13}H_9N$, melting at 275°, results from the reduction of *α*-**anthrapyridine quinone,** $C_6H_4<_{CO}^{CO}>C_6H_3N$, melting at 280°, which is made by condensing *β*-benzoylpicolinic acid with sulphuric acid. *β*-**Anthrapyridine,** melting at 166°, is similarly formed from *β*-**anthrapyridine quinone,** the condensation product of *γ*-benzoyl nicotinic acid (B. **28,** 1658).

VEGETABLE ALKALOIDS.*

Formerly, all nitrogen-containing bodies occurring in plants and possessing basic, alkaline character, or derivatives of the same, from which bases could be isolated, were designated as alkaloids.

Many of them (*betaïne, asparagine, caffeïne, theobromine, hordenine, stachhydrine*, etc.) have, in accord with their constitution, been already discussed with the various amino-derivatives; most of those remaining which have been studied recently show themselves to be derivatives of pyridine, quinoline, and *iso*quinoline, and the name " vegetable alkaloids " is usually reserved for these.

Several of the alkaloids dealt with below are derivatives of other heterocyclic nuclei. Thus *morphine*, the oldest known alkaloid, turns out to be a derivative of a complicated heterocyclic nucleus not hitherto synthesized, while *hygrine* is a derivative of pyrrolidine and *pilocarpine* a derivative of glyoxaline, etc. A more general definition of a vegetable alkaloid is " a basic compound occurring in nature, in which at least one N atom forms part of a cyclic system " (Ladenburg, A. **301,** 117).

These vegetable alkaloids are usually the active constituents of vegetable drugs officially classed as medicines or poisons.

Because of their great number and their often unusually remarkable physiological and pharmacological properties they constitute one of the most interesting classes of carbon compounds.

Occurrence.—The vegetable alkaloids occur almost exclusively in the dicotyledons. Of the alkaloids described below, only veratrine, betel nut essence, and the poorly investigated *colchicine* are formed in monocotyledons, while the large families of the Compositæ and Labiatæ do not furnish them. In plants they are generally combined with widely distributed *plant acids—e.g., malic acid, citric* or *aconitic acid*, and *tannic acid*. Many are accompanied by acids which usually are found associated with definite alkaloids—*e.g.*, the opium alkaloids are united with meconic acid (p. 150), and the cinchona alkaloids with *quinic acid*. The alkaloids prized for their pharmacological properties are the subject of technical isolation. The artificially prepared carbon compounds, having similar physiological action, hold a subordinate position compared with them—*e.g.*, quinine and *antipyrine;* atropine and several *tropeins;* cocaine and *eucaine*.

On the generation of alkaloids in plants, see Bull. soc. Ch. [3], **35,** 15; B. **44,** 2032.

Some alkaloids contain no oxygen, and then are generally liquid and volatile—*e.g., piperidine, coniine, nicotine*, and *sparteïne*. Most of them do, however, contain that element, and are solid and non-volatile. Nearly all are tertiary amines; some, however (like the hydrides of the pyridine nucleus), belong to the secondary amines. Many (like *pilocarpine*) are ammonium bases. Tannic acid, phosphomolybdic acid, platinic chloride, and many double salts (like $HgI_2.KI$) precipitate all these bases from their aqueous solutions. The bases are regained from these compounds by alkalies.

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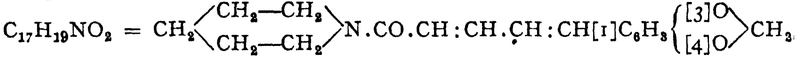
* Consult " La Constitution chimique des Alcaloïdes végétaux," par Amé Pictet. Paris, G. Masson, 1897 (II. ed.).

The alkaloids have a more or less bitter taste. Most of them are optically active and, generally, lævorotatory (I. 54). *Coniine, narcotine,* and *pilocarpine* are dextrogyratory. Piperine is inactive. Many alkaloids give characteristic colours with chlorine water, nitric acid, or concentrated sulphuric acid.

THE PYRIDINE GROUP OF THE VEGETABLE ALKALOIDS.

Piperine,



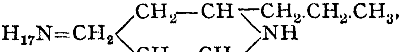
$$C_{17}H_{19}NO_2 = CH_2\left<\begin{matrix}CH_2-CH_2\\ CH_2-CH_2\end{matrix}\right>N.CO.CH:CH.CH:CH[1]C_6H_3\left\{\begin{matrix}{[3]O}\\ {[4]O}\end{matrix}\right>CH_2$$

melting at 128°, occurs in different varieties of pepper, the fruit of *Piper nigrum* and *Piper longum*. It dissolves with a deep red colour in sulphuric acid. It is decomposed by boiling alcohol into piperidine and piperic acid.

The two decomposition products of piperine have been built up from their elements, and by allowing the chloride of piperic acid to act upon piperidine the synthesis of piperine itself has been realized (B. **27,** 2958). The synthesis of coniine presupposes that of piperidine, and is represented by diagram under coniine. Artificial piperines have been prepared from the synthetic *α*-alkyl and *α*-phenyl piperic acids with the assistance of the chlorides (B. **28,** 1195).

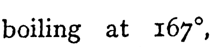
Tetrahydropiperine, $C_{17}H_{23}NO_3$, b.p.$_{16}$ 280° (see B. **44,** 2942).

α-**Coniine,** d,*α*,n-*propylpiperidine,*



$$C_8H_{17}N = CH_2\left<\begin{matrix}CH_2-CH-CH_2.CH_2.CH_3,\\ \qquad\qquad NH\\ CH_2-CH_2\end{matrix}\right.$$

boiling at 167°, with sp. gr. 844 (20°), $[\alpha]_D = +15·7$ at 19° (B. **27,** 3062), occurs, together with *N*-methylconiine and *γ*-coniceïne,



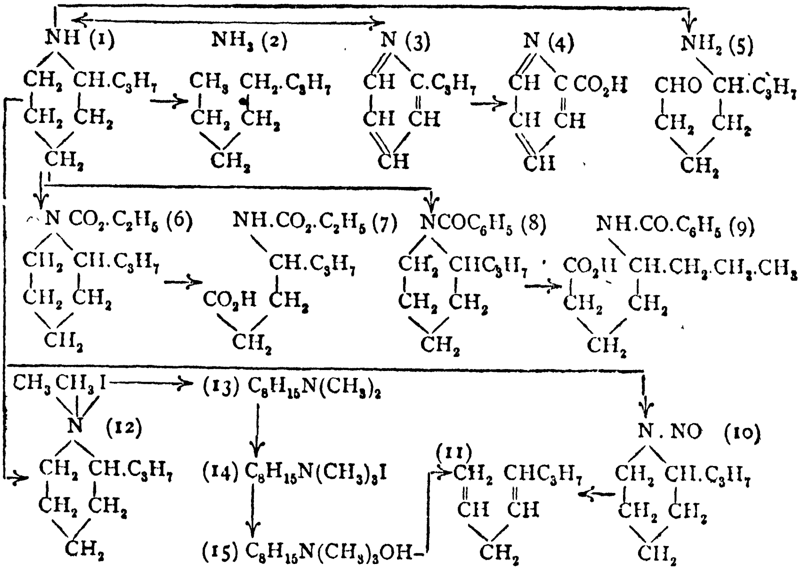
$$CH_2\left<\begin{matrix}CH = C(C_3H_7)\\ CH_2-CH_2-\end{matrix}\right>NH$$

(B. **28,** 302, synthesis; B. **42,** 4059), conhydrine and *pseudo*-conhydrine, in hemlock (*Conium maculatum*), especially in the seeds. On the separation of these alkaloids, see B. **38,** 3018. Coniine is a colourless liquid with a stupefying odour. It is a very powerful poison.

History.—Giesecke (1827) discovered coniine. A. W. Hofmann (1881) determined its molecular weight, and in 1884 demonstrated that it yielded conyrine or *α*-propylpyridine upon distillation with zinc dust. Obtaining picolinic acid by oxidation, he thus proved the *α*-position of the propyl group. The synthesis of optically inactive coniine, its decomposition into *d*- and *l*-coniine, and thereby the first complete synthesis of an optically active alkaloid, are due to Ladenburg (1886) (B. **22,** 1403).

The following diagrams represent the decomposition of coniine, which corresponds to that of piperidine, and also the synthesis, which presupposes that of piperidine and pyridine.

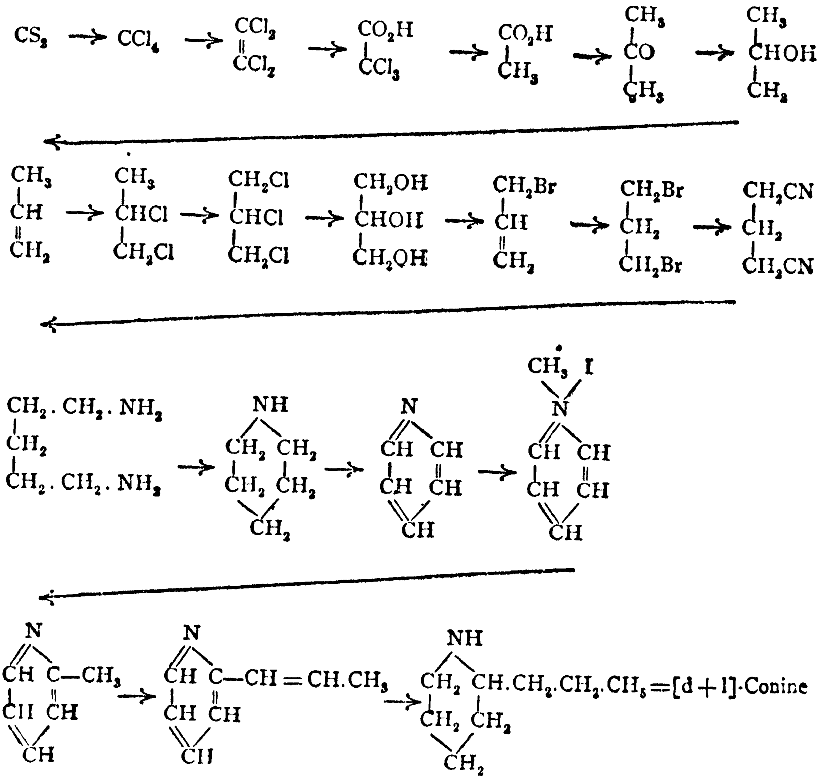
Decomposition of Coniine.—The reduction of natural *d*-coniine (1) by hydriodic acid resolves it into *n*-octane (2) and ammonia (B. **18,** 13). The distillation with zinc dust leads to conyrine (3), or *α,n*-propyl pyridine, which hydriodic acid reduces to inactive [*d* + *l*]-coniine, while upon oxidation it becomes picolinic acid (4) or pyridine-*α*-carboxylic acid. Hydrogen peroxide oxidizes coniine to δ-amino-*n*-octoic aldehyde, or amino δ-propylvaleraldehyde (5) (B. **28,** 1460). Nitric acid oxidizes conylurethane (6) to carbethoxyconinic acid or γ-carboethylamino-*n*-heptoic acid (7) (B. **15,** 1947), which yields coninic acid when heated with hydrochloric acid. Potassium permanganate oxidizes benzoyl coniine to benzoyl homoconinic acid or δ-benzoylamino-*n*-octoic acid (8) and benzoyl-α-aminovaleric acid (9) (B. **19,** 502). Nitrous acid converts coniine into nitroso-coniine (10), which breaks down, on heating with phosphorus pentoxide, into water, nitrogen, and conylene (11). Methyl iodide and coniine combine to dimethylconinium iodide (12), which is changed by sodium hydroxide to dimethylconiine, $C_8H_{15}N(CH_3)_2$ (13). The latter is not homogeneous, but consists of a little methylconiine and a mixture of two isomeric bases formed by the splitting of the piperidine ring between the N and the α-C-atom and between N and the $α_1$-C-atom respectively. With methyl iodide they combine to form iodides (14), which with silver oxide yield the so-called trimethyl coninium hydroxide, $C_8H_{15}.N(CH_3)_3(OH)$ (15), which on distillation splits up into water, trimethylamine, and conylene (11). With HI, dimethylconiine combines energetically. Reduction of the hydroiodide produces a mixture of two saturated bases, one of which has been identified as dimethyl-normal-octylamine through its iodomethylate (A. **298,** 131).



Synthesis of Coniine (B. **22,** 1404; **40,** 3734).—We start with the synthesis of glycerin, which may be undertaken either by way of acetic acid or of nitro-methane (Vol. I.). Glycerin is converted into ally bromide. Allyl bromide and hydrobromic acid combine to trimethylene bromide, the latter yielding, by way of trimethylene cyanide and reduction, pentamethylenediamine, from which piperidine results by the elimination of ammonia (I. 334). Piperidine may be oxidized to pyridine, the iodo-methylate of which—pyridinium iodide—is changed at 300° into α-picoline iodo-hydrate.

α-Picoline condenses with paraldehyde to α-methylpicolylalkine, which is converted by successive treatment with HI and Zn dust into α,*n*-propylpyridine, or by heating with concentrated HCl into α-propenyl pyridine. The latter can also be obtained by heating α-picoline with paraldehyde to high temperatures. Reduction of α-propyl- or α-propenylpyridine with Na and alcohol produces inactive coniine.

***d*-Coniine *d*-tartrate** separates first from a solution of dextro-tartrate of inactive coniine; and caustic potash resolves it into a *coniine identical* with the *natural coniine*. As dextro-tartaric acid can be prepared from synthetic racemic acid, the synthesis of coniine is complete.



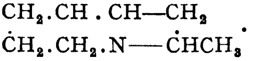
CS₂ → CCl₄ → CCl₂=CCl₂ → CO₂H.CCl₃ → CO₂H.CH₃ → CH₃.CO.CH₃ → CH₃.CHOH.CH₃
CH₃.CH=CH₂ → CH₃.CHCl.CH₂Cl → CH₂Cl.CHCl.CH₂Cl → CH₂OH.CHOH.CH₂OH → CH₂Br.CH=CH₂ → CH₂Br.CH₂.CH₂Br → CH₂CN.CH₂.CH₂CN
CH₂.CH₂.NH₂ / CH₂ / CH₂.CH₂.NH₂ → NH → N → CH₃ I N
CH—CH₃ → C—CH=CH.CH₃ → NH / CH.CH₂.CH₂.CH₃=[d+l]-Conine

***d*-Coniine Hydrochloride** melts at 218°. **Nitroso-*d*-coniine** is a bright yellow-coloured oil. ***d*-Conyl Urethane** boils at 245°. **Benzoyl-*d*-coniine** is a thick oil.

The inactive *r*- (racemic) or *d*+*l*-coniine and the *l*-coniine behave chemically and physiologically like *d*-coniine. Inactive coniine is best formed by the reduction of γ-coniceïne (B. **29**, 1956).

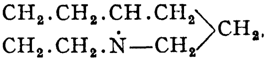
Besides coniine, we find in hemlock the two isomeric oxygenated alkaloids **conhydrine,** m.p. 120°, b.p. 226°, and *pseudo*-**conhydrine,** m.p.

106°, b.p. 236°. The former should be regarded as one of the optically active forms of α-ethyl piperyl alkine, $(C_5H_9NH)CH(OH)CH_2CH_3$, and the latter as a coniine hydroxylated in the piperidine nucleus. Successive treatment with HI and zinc dust converts conhydrine into *l*-coniine, and *pseudo*-conhydrine into *d*-coniine. On extracting water from conhydrine by means of P_2O_5 or concentrated HCl we obtain small quantities of γ-coniceïne, which occurs in nature, as well as the isomeric β-coniceïne or ***l*,α-propenyl-piperidine,** $(C_5H_9NH)CH:CH.CH_3$, in two probably stereo-isomeric forms. The iodide formed from this by attachment of HI yields, on treatment with alkali, by intramolecular alkylation the tertiary, saturated, bicyclic **ϵ-coniceïne,**



$$\begin{array}{l} CH_2.CH\,.\,CH{-}CH_2 \\ \dot{C}H_2.CH_2.N{-}\dot{C}HCH_3 \end{array}.$$

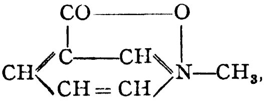
Isomeric with these bases is **δ-coniceïne,**



$$\begin{array}{l} CH_2.CH_2.CH.CH_2 \\ CH_2.CH_2.\dot{N}{-}CH_2 \end{array}\!\!\Big\rangle CH_2,$$

which has been obtained from coniine by bromination with hypobromite and subsequent detachment of HBr by means of concentrated H_2SO_4. Compare the corresponding optically inactive forms of these bases (B. **42,** 94, 929).

Trigonelline, *Nicotinic Acid Methyl Betaïne,*



melting at 218°, occurs in the seeds of *Trigonella fœnum græcum,* and in small amount, together with choline, in the seeds of *Pisum sativum;* also in hemp (*Cannabis sativa*), in some species of *Strophanthus* (B. **31,** 271), and of the coffee plant (A. **372,** 239). As Jahns has shown, trigonelline is identical with nicotinic acid betaïne, synthesized by Hantzsch (1886) (B. **27,** 769).

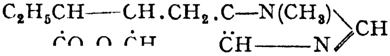
Arecaïdine, N-*Methyl-tetrahydronicotinic Acid,* $C_5H_8(COO)N.CH_3$-$(+H_2O)$, melting at 224°, occurs, together with **arecoline,** $C_8H_{13}NO_3$ (chief constituent), **arecaïne,** $C_7H_{11}NO_2$, and **guvacine,** $C_6H_9NO_2$, in the nut of *Areca catechu.* It has been obtained synthetically from *N*-methyl-Δ^β-tetrahydro-pyridine aldoxime by conversion into the nitrile and saponification (B. **40,** 4712). It is also formed, together with its dihydro-derivative, **dihydro-arecaïdine** or N-*methyl-hexahydronicotinic acid,* from the chloromethylate of nicotinic acid ester by reduction with zinc and HCl. It forms **arecoline,** boiling at 209°, when treated with methyl alcohol and HCl (esterified), which by saponification yields arecaïdine, and it is therefore *tetrahydro*-N-*methylnicotinic methyl ester* (B. **25,** R. 198; **30,** 729; C. 1902, I. 821). The constitution of arecaïne and guvacine has not yet been definitely established.

Pilocarpine, $C_{11}H_{16}N_2O_2, [\alpha]_D = +101{\cdot}6°$, and **Pilocarpidine,** $C_{10}H_{14}N_2O_2$, occur in the Jaborandi leaves of *Pilocarpus pennatifolius.*

Pilocarpine is a poison which acts like nicotine (A. **238,** 230). The injection of it into milch cows occasions a very appreciable increase in the sugar of the milk (B. **26,** R. 247).

The constitution of pilocarpine and pilocarpidine, formerly regarded as known, is still, according to recent researches, undetermined. Pilocarpine contains a methyl group attached to N, and this is absent in pilocarpidine. Pilocarpine is easily converted into an isomeric base, *iso*pilocarpine—*e.g.*, by heating its hydrochloride. On the other hand, *iso*pilocarpine, on heating with alcoholic potash, passes partly into pilocarpine (C. 1905, II. 140). Pilocarpine and *iso*pilocarpine are lactones. With NaHO they yield the corresponding oxy-carboxylic acids. With Br they yield dibromopilocarpine and *iso*dibromopilocarpine. While the alkaloids themselves are stable in the presence of alkalies, their halogen alkylates are broken up by boiling with potash, forming methylamine and alkylamine, in accordance with the alkyl haloid used (compare the analogous behaviour of the glyoxaline derivatives). Since, in addition, the distillation of the alkaloids with soda lime produces alkylated glyoxalines, it is probable that pilocarpine and *iso*-pilocarpine contain the ring of *n*-methylglyoxaline.

By oxidation with CrO_3, pilocarpine gives pilocarpoic acid, $C_{11}H_{16}N_2O_5$. With permanganate, pilocarpine and *iso*pilocarpine give the lactonic acids, $C_8H_{12}O_4$ and $C_7H_{10}O_4$, homopilopic acid, and pilopic acid. Homopilopic acid, fused with potash, gives *α*-ethyl-tricarballylic acid, which is also obtained from pilocarpoic acid by further oxidation with $KMnO_4$. From these data the following provisional formula has been derived for pilocarpine:



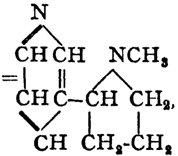
$$\begin{array}{l} C_2H_5CH—CH.CH_2.C—N(CH_3) \\ \quad CO\;\;O\;\;CH \qquad\quad CH——N \end{array} \!\!> CH$$

(B. **35,** 2441; **38,** 1510; C. 1901, I. 1059; 1903, I. 930).

Cytisine, *Ulexine, Sophorine,* $C_{11}H_{14}N_2O$, melting at 152°, occurs in the seeds of *Cytisus laburnum,* as well as in other Cytisus varieties, in *Ulex europæus,* and in *Sophora tomentosa* and *speciosa* (B. **23,** 3201; **24,** 634; **27,** R. 509, 884; **28,** R. 237; **29,** R. 36, 53; C. 1900, II. 268).

Cytisine contains an imide group. Its acetyl compound melts at 174°, its benzoyl compound at 116°. With concentrated HNO_3 it yields nitro-nitroso-cytisine, which, by splitting off a nitroso-group, may be converted into nitro-cytisine and further into amino-cytisine. H_2O_2 oxidizes it to oxycytisine, $C_{11}H_{14}N_2O_2$. HI and phosphorus yield, beside other products, **cytisoline,** $C_{11}H_{11}NO$, m.p. 199°, which is oxidized by CrO_3 to cytisolinic acid, $C_{11}H_9NO_3$, and is reduced by Na and alcohol to *α*-**cytisolidine,** $C_{11}H_{15}N$. By electrolytic reduction cytisine gives the base $C_{11}H_{22}N_2$ (B. **39,** 818). In the seed of *Anagyris fœtida* we find both cytisine and the closely related **anagyrine,** $C_{15}H_{22}N_2O$ (C. 1900, I. 1162).

Nicotine, *α-Pyridyl-β-tetrahydro-N-methylpyrrole,* $C_{10}H_{14}N_2$=



boiling at 247°, with sp. gr. 1·011 (15°), and $[\alpha]_D^{20} - 169{\cdot}22°$ (C. 1906, I. 474), occurs in the leaves of the tobacco plant, *Nicotiana tabacum,* in quantities varying from 0·6 to 8 per cent., depending upon the varieties. As a rule, the better qualities of tobacco contain less nicotine than the poorer sorts.

Certain subsidiary alkaloids are found in tobacco lye: **Nicoteïne,** $C_{10}H_{12}N_2$, b.p. 267°, $[\alpha]_D - 46{\cdot}41°$, a di-tertiary base, which on oxidation gives nicotinic acid; **nicotelline,** $C_{10}H_8N_2$, m.p. 148°; and **nicotimine,**

$C_{10}H_{14}N_2$, b.p. 150° to 155°, a tertiary-secondary base isomeric with nicotine; and small quantities of pyrrolidine and *N*-methylpyrroline (B. **34,** 696; **40,** 3773; C. 1906, II. 1619).

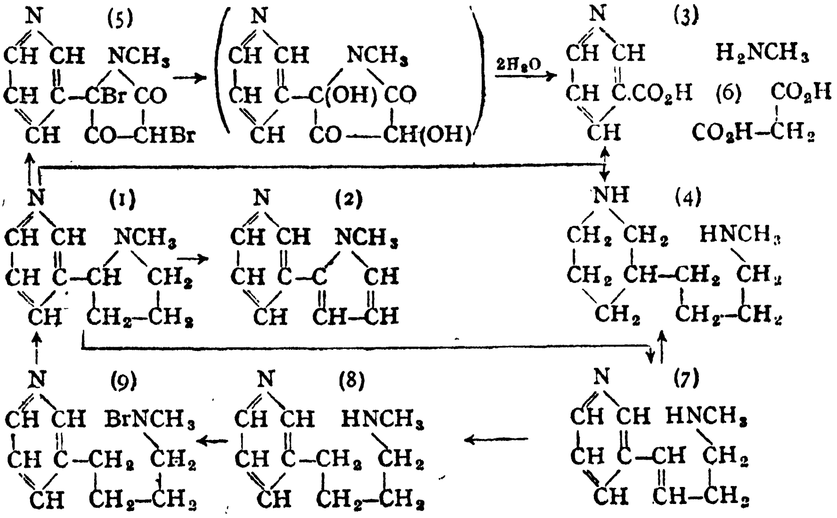
Nicotine is very soluble in water. It has a disagreeable odour and burning taste. It is a violent poison.

History.—Posselt and Reiman discovered nicotine (1828). Since 1891 Blau, but more especially Pinner, has studied its transposition reactions. The constitutional formula proposed by Pinner harmonizes with its behaviour, and has more recently been fortified by the experiments of Amé Pictet and Crépieux (1895), which have led to the synthesis of nicotine.

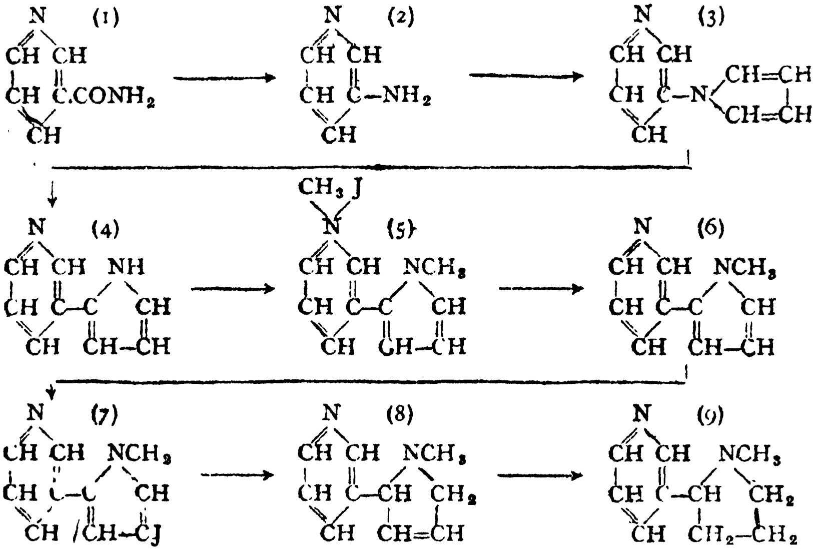
Nicotine (1) is a di-tertiary base, with dextro-rotatory salts. It gives a di-iodomethylate and two isomeric mono-iodomethylates, one of which on oxidation yields trigonelline.

Potassium ferricyanide, or, better, silver oxide, oxidizes nicotine to nicotyrine (2) or α-β-pyridylmethylpyrrole (B. **27,** 2535). Nitric acid, chromic acid, or potassium permanganate oxidizes it to nicotinic acid (3) or β-pyridine carboxylic acid (A. **196,** 130; see also B. **30,** 2122). Sodium and alcohol reduce it to hexahydronicotine and, with rupture of the pyrrolidine ring, octohydro-metanicotine (4) (B. **26,** 765). With bromine and water nicotine forms *dibromonicotine* (5), $C_{10}H_8Br_2N_2O_2$, which baryta-water resolves into methylamine, malonic acid (6), and nicotinic acid (B. **26,** 292). Nicotine takes up benzoyl chloride. Hydrochloric acid liberates nicotine from the addition-product, while sodium alcoholate produces a secondary base, *metanicotine,* isomeric with nicotine and melting at 275°–278°. It is probably ω-methylamino-propylidene-β-picolin.

Reduced with sodium and alcohol, this yields hexahydro-metanicotine and octohydrometanicotine (4). With HI and red phosphorus dihydrometanicotine (8), from which sodium hypobromite forms dihydrometanicotine (9) brominated at the nitrogen; the latter, heated with concentrated H_2SO_4, splits off HBr and forms nicotine (1):



Synthesis of Nicotine (see scheme below).—Nicotinic acid amide (1) gives with potassium hypobromite β-aminopyridine (2), which, distilled with mucic acid, gives *N,β*-pyridylpyrrole (3). Conducted through a feebly incandescent tube, the latter turns into αβ-pyridyl pyrrole (4), which, with methyl iodide, gives nicotyrine iodo-methylate (5) (B. **28,** 1909). The latter is converted into nicotyrine (6) by distillation with CaO. For reconverting nicotyrine into nicotine the following procedure was adopted: Nicotyrine, treated with iodine, gives iodonicotyrine (7), and this, reduced with zinc dust and NaHO, dihydronicotyrine (8). On reducing the bromination product of the latter with tin and HCl it is converted into tetrahydro-nicotyrine (9), a base identical with the *inactive* nicotine obtained on heating nicotine salt solutions to 180°–250°. Inactive nicotine (tetrahydronicotyrine) can, by means of its bitartrate, be split up into *l*-nicotine, identical with natural nicotine, and *d*-nicotine $[\alpha]_D + 163{\cdot}17°$, which is much less poisonous than natural nicotine (B. **37,** 1225; Bull. soc. chim. [3], **35,** 1):

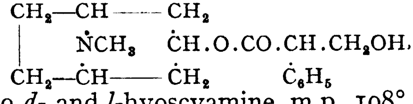


Sparteïne, $C_{15}H_{26}N_2$, b.p. 325°, D_{20} 1·02, $[\alpha]_D - 16{\cdot}42°$, is a colourless thick oil contained in the broom, *Spartium scoparium,* and, besides **lupinine,** $C_{10}H_{19}ON$, in *Lupinus luteus* and *Lupinus niger.* Sparteïne is a saturated, di-acid, di-tertiary base, containing no free methyl group attached to the nitrogen. Since the presence of an aromatic nucleus is improbable, we must assume the existence of *four* saturated rings. On oxidation with chromic acid or alkaline potassium ferricyanide solution it yields **oxy-sparteïne,** $C_{15}H_{24}N_2O$; with H_2O_2, **sparteïne oxide,** $C_{15}H_{24}N_2O_2$, from which sparteïne is easily regenerated; with chromic acid we also obtain an unsaturated base, **spartyrine,** $C_{15}H_{24}N$, and a neutral compound, $C_{15}H_{24}N_2O_4$ (B. **37,** 3238; **38,** 1772, 3268). The methylsparteïnium hydroxide obtained from sparteïne iodomethylate with moist silver oxide decomposes, on heating with water, into a mixture of two unsaturated bases methylated at the nitrogen, $C_{15}H_{25}N_2CH_3$: **α-methylsparteïne,** m.p. 31°, and **β-methylsparteïne,** liquid. The haloid salts of α-methylsparteïne isomerize in various conditions to the halogen methylates of a new base, the so-called *iso-sparteïne*, $C_{15}H_{26}N_2$. On the other hand, the methyl*iso*sparteïnium hydroxide, on heating, splits off water and regenerates α-methyl sparteïne. These reactions, analogous to the conversion of methyl piperidine into dimethylpyrrolidine, seem to prove the presence of at least one piperidine nucleus in sparteïne (Bull. soc. chim. [4], **3,** 674, **5,** 31). An alkaloid apparently closely related to sparteïne, **lupanine,** $C_{15}H_{24}N_2O$, has been found in some varieties of lupins.

II. TROPINE GROUP.

Solanum Bases.—Several very similar alkaloids are found in many varieties of solanum, of which the best known are the two isomerides: optically inactive *atropine*, discovered by Mein in 1833, as well as by Gieger and Hesse, and lævorotatory *hyoscyamine*. If they are introduced in very small quantity into the eye they cause dilatation of the pupil, and are therefore used in medicine as *mydriatics*. Both bases are found in *Hyoscyamus niger* and *albus*, in *Datura stramonium*, in the "deadly nightshade," *Atropa belladonna*, and in *Duboïsia myoporoïdes*; hyoscyamine also in the mandragora root (B. **31,** 2031). The less investigated bases which accompany them are *belladonine* (B. **17,** 152, 383), *hyoscine, scopolamine* (B. **25,** 260; **29,** 1771, 2099, 2439), *apoatropine* (below) (B. **25,** R. 573; **26,** R. 285), all of which, as acid decomposition products, yield tropic and atropic acids; as basic constituents they yield bodies closely allied to tropine.

Atropine = [*d* + *l*]-**Hyoscyamine,**



$$\begin{array}{lll} CH_2—CH & —— & CH_2 \\ |\quad\quad \dot{N}CH_3 & & \dot{C}H.O.CO.CH.CH_2OH. \\ CH_2—\dot{C}H & —— & CH_2 \quad\quad \dot{C}_6H_5 \end{array}$$

m.p. 115°, may be decomposed into *d*- and *l*-hyoscyamine, m.p. 108°, by means of its *d*-camphor-sulphonate (C. 1910, I. 541). The *l*-hyoscyamine is contained with atropine in many plants. This body racemizes in part to atropine on treatment with aqueous or alcoholic sodium hydroxide (B. **21,** 1717, 2777, 3069; C. 1901, I. 129). It is very probable that the two bases are physical isomerides. Atropine is decomposed into *tropine* and *tropic acid*, or *α-phenylhydracrylic acid*, $CH_2OH.CH(C_6H_5)CO_2H$ (II. 380), when it is heated with hydrochloric acid or baryta-water. Conversely, atropine is formed when tropic acid and tropine are evaporated with dilute hydrochloric acid (Ladenburg), or by transposition of tropine with acetyl-tropic acid chloride and rejection of the acetyl group (B. **41,** 726). Analogously, *l*-hyoscyamine decomposes on saponification with water into *i*-tropine and *l*-tropic acid, and can be synthesized from these by evaporating with dilute HCl (C. 1902, II. 1327).

Apoatropine, *Atropamine*, $C_{17}H_{21}NO_2$, melting at 60°–62°, results from the action of nitric acid upon atropine. It is made synthetically by evaporating tropine atropate with dilute hydrochloric acid. It is decomposed by baryta-water into tropine and atropic acid (II. 425); it is the *tropeïne* of atropic or α-phenylacrylic acid.

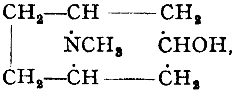
Tropeïnes.—Just as tropine yields atropine with atropic acid, so it is capable of entering into combination with other acids producing ester-like derivatives, which have been called *tropeïnes* (Ladenburg, A. **217**, 82; **27,** R. 202). Of these, phenylglycollyltropeïne, or **Homatropine,** $C_5H_7N(CH_3).C_2H_4.O.CO.CH(OH).C_6H_5$, is noteworthy because its mydriatic action is not so prolonged. It is obtained from tropine and mandelic acid. It is employed as a substitute for atropine, and is applied in the form of hydrobromide. It melts at 95·5°–98·5°.

Only those tropeïnes possess mydriatic action in which the acid radical contains alcoholic hydroxyl (but compare C. 1909, II. 542).

Lactyltropeïne melts at 74° (B. **28,** R. 492).

Benzilo-tropeïne is the tropeïne of benzilic acid (p. 367) (B. **27,** R. 202). See also *Euphthalmine,* the mandelic acid ester of *N*-methyl-vinyl diacetone alkamine.

Tropine,



$$\begin{array}{l} CH_2\text{—}CH\text{——}CH_2 \\ \big|\quad\ \ NCH_3\quad CHOH \\ CH_2\text{—}CH\text{——}CH_2 \end{array}$$

, melting at 62° and boiling at 233°, is the basic decomposition product of atropine. According to Willstätter, it is an *N*-methyl-γ-oxypiperidine, the α- and α_1-carbon atoms of which are joined by the group —CH_2—CH_2—. It would thus contain also the pyrrolidine ring and a carbon seven-ring, and would have to be regarded as a derivative of suberane. *Ecgonine,* the basic decomposition product of cocaine, is a tropine carboxylic acid. These inter-relations explain the many similarities in the action of atropine and cocaine.

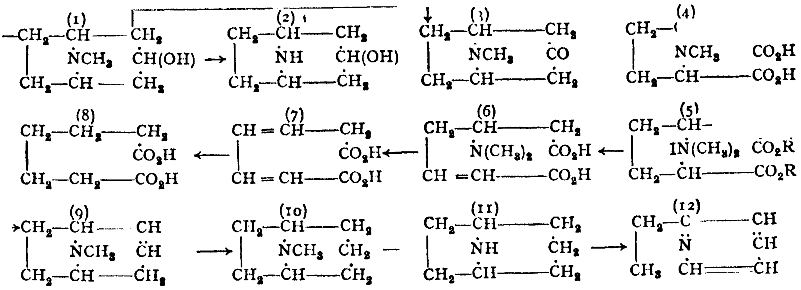
The chief reason for the above formula for tropine was the observation that tropinone, the first oxidation product of tropine, yields a dibenzal- and a di-*iso*nitroso-compound, etc., and must therefore contain the group —$CH_2.CO.CH_2$— (B. **31,** 1537).

The constitution of tropine and ecgonine follows further from its decomposition reactions, mostly effected by Hofmann's iodomethylate method. We are indebted mainly to Ladenburg, Merling, Einhorn, and Willstätter for our knowledge of these.

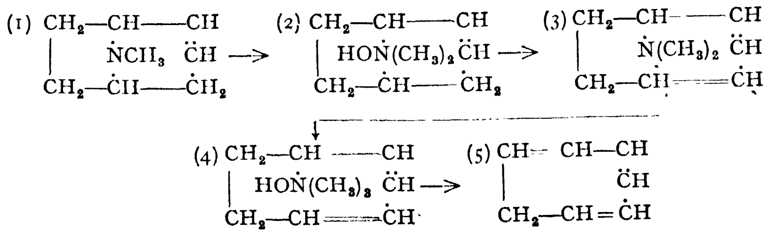
Decomposition of Tropine.—(*a*) *Conversion of tropine into tropic acid, and into α-ethylpyridine and picolinic acid.* Potassium permanganate oxidizes tropine (1) to tropigenine (2), whereas with chromic acid it first yields a ketone, tropinone (3), which upon reduction does not yield tropine again, but a ψ-tropine, which is always obtained by the decomposition of an alkaloid associated with cocaïne (B. **33,** 1170).

On further oxidation with CrO_3, tropinone yields tropinic acid (4), or *N*-methylpyrrolidine -$\alpha\alpha_1$-acetic-carboxylic acid. The tropinic acid ester iodo-methylate (5) is split up by alkali to methyl tropinic acid (6), the iodo-methylate of which, again treated with alkali, is changed into piperylene dicarboxylic acid (7). Reduction of the latter produces normal pimelic acid (8).

(*b*) Glacial acetic acid and HCl deprive tropine of water and produce tropidine (9), which on oxidation with permanganate passes into dihydroxy-tropidine. The latter, on further oxidation, also yields tropinic acid (4) (B. **28,** 2277). On reducing tropidine with Zn and HCl, it becomes hydro-tropidine or tropane (10), which is also obtainable from tropinone (3) (B. **33,** 1173), and forms norhydro-tropidine (11) on heating its hydrochloride in a stream of HCl. On distilling (11) over zinc dust we obtain α-ethylpyridine (12), which on oxidation yields α-picolinic acid (B. **20**, 1647):

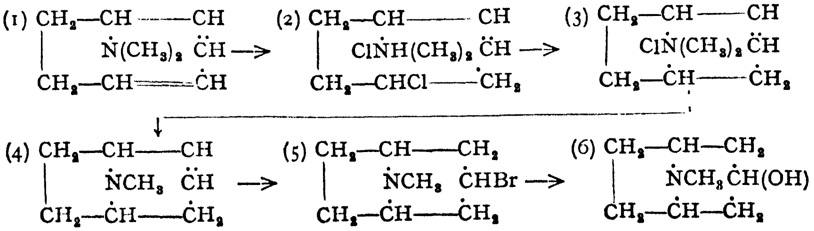


(*c*) *The conversion of tropidine into tropilidene or* cyclo-*heptatriene* (B. **31**, 1542). Tropidine (1) adds methyl iodide, and the iodo-methylate, treated with moist silver oxide, gives methyl tropidinium hydroxide (2), which, on boiling with water, turns into methyltropidine or dimethyl amino-*cyclo*-heptadiene (3). The latter, treated in the same manner as tropidine, yields dimethyl tropidinium hydroxide (4) and tropilidene or *cyclo*-heptatriene (5):

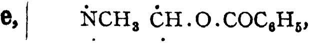


In a similar manner, hydrotropidine has been split up to form *cyclo*-heptadiene; also, the **tropilene** obtained by the thorough methylation of tropidine is $C_7H_{10}O$,Δ^2-*cyclo*-heptenone, while the compound C_7H_8O, obtained by the disintegration of tropinone iodo-methylate, must be regarded as a dihydro-benzaldehyde, since by oxidation it yields dihydro-benzoic acid (B. **44**, 464).

Synthesis of Tropine.—Methyltropidine or dimethylamino-*cyclo*-heptadiene (1) adds 2HCl and forms hydro-chloro-methyl-tropidine hydrochloride (2). This, with NaHO, splits off HCl and gives tropidinium chloro-methylate (3), which on distillation splits up into tropidine (4) and methyl chloride. Tropidine, by adding HBr and heating the resulting bromo-tropane (5) with dilute mineral acid, is converted into tropine (6) (A. **326**, 1):

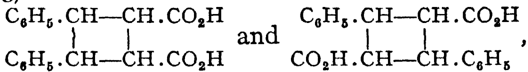


Similarly, methyl-tropane or dimethylamino-*cyclo*-heptene is convertible into tropane. These syntheses have been completed by building up methyl-tropidine and methyl-tropane from the *cyclo*-heptatriene (tropilidene) and *cyclo*-heptene, which are accessible through synthetic suberone (B. **34,** 129; A. **317,** 307).

l-**Cocaïne,** 

$$\begin{array}{l} CH_2—CH—CH.CO_2CH_3 \\ |\qquad \dot{N}CH_3\ \dot{C}H.O.COC_6H_5 \\ CH_2—\dot{C}H—\dot{C}H_2 \end{array}$$

m.p. 98°, lævo-rotatory, is contained in the leaves of *Erythroxylon coca.* It is an excellent local anæsthetic, and is employed in the form of an HCl salt. On heating with HCl it decomposes into ecgonine, benzoic acid, and methyl-alcohol and, on boiling with water into benzoylecgonine and methyl alcohol. Conversely, cocaïne can be built up from ecgonine, benzoyl ecgonine, and ecgonine methyl ester, by either benzoylating ecgonine methyl ester or esterifying benzoylecgonine with methyl alcohol. In this way certain alkaloids—*e.g., cinnamylcocaïne, truxilline,* etc. —associated with cocaïne (B. **27,** 783 n.) become valuable technically. In their decomposition they yield ecgonine methyl ester and ecgonine (B. **22,** 2960, R. 953).

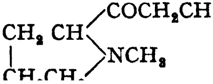
Truxillic Acids, 

$$\begin{array}{l} C_6H_5.CH—CH.CO_2H \\ \qquad\ \ |\qquad\ | \\ C_6H_5.CH—CH.CO_2H \end{array} \quad \text{and} \quad \begin{array}{l} C_6H_5.CH—CH.CO_2H \\ \qquad\ \ |\qquad\ | \\ CO_2H.CH—CH.C_6H_5 \end{array}$$

, poly-cinnamic acids, dicinnamic acids, and also *allo*cinnamic acid, were discovered by Liebermann in his study of the secondary alkaloids of cocaïne. By distillation they yield ordinary cinnamic acid. The *a-acid* melts at 274°; the *β-acid* at 206°. Acetic anhydride and sodium acetate convert the first into the anhydride (m.p. 191°) of *γ-truxillic acid,* melting at 228° (B. **22,** 126). When the *β-acid* is fused with caustic potash it changes to *δ-truxillic acid,* melting at 174°. Potassium permanganate oxidizes the *β*-acid to benzil (B. **22,** 2254)—a reaction which, together with the inability to take up bromine and the stability of *β*-truxillic acid toward cold potassium permanganate, argues for the constitutional formula given above (B. **27,** 1410).

d-**Cocaïne,** melting at 43°–45°, occurs in small quantities in the mixed cocaïne bases (B. **23,** 926). It is obtained synthetically from *d*-ecgonine (B. **23,** 982). See B. **27,** 1874, 1880, for cocaïnes substituted in the benzoyl group.

Tropa-cocaïne, *Benzoyl-ψ-tropine,* $C_{15}H_{19}NO_2$, melting at 49°, and found in small amounts in the coca alkaloids, breaks down into benzoic acid and **ψ-tropine,** melting at 108° and boiling at 241°. The latter appears to be a stereoisomeride of tropine, because it can also be prepared by the reduction of tropinone, and when oxidized reverts to the latter. Indeed, tropine can be directly rearranged to ψ-tropine by means of sodium amylate. Potassium permanganate oxidizes ψ-tropine to ψ-tropigenine, which, like tropigenine, yields nortropinone upon oxidation (B. **29,** 936, 1636, 2231).

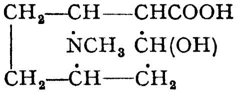
Mention may also be made here that crude cocaïne contains small quantities of **Hygrine,** $C_8H_{15}NO$, boiling at 92°–94° (20 mm.). It is a derivative of *N*-methylpyrrolidine, probably 

$$\begin{array}{l} CH_2\ CH\!\!\begin{array}{l}\diagup COCH_2CH_3 \\ \diagdown \end{array} \\ |\qquad\qquad\ \ >NCH_3 \\ CH_2CH_2\diagup \end{array}$$

, as

it forms an oxime, and when oxidized becomes *hygric acid*, or *N*-methylpyrrolidinecarboxylic acid, which parts with carbon dioxide very readily (B. **28,** 578).

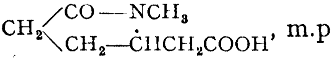
l-**Ecgonine,** *Tropinecarboxylic Acid,*



melts at 205° when anhydrous. It is the basic decomposition product of *l*-cocaïne. When digested with caustic potash it changes to d-*ecgonine*, melting at 254°. See B. **24,** 7; **26,** 962, for the esters, amides, and nitriles of the ecgonines.

For iodalkylates, see J. pr. Ch. [2], **65,** 91.

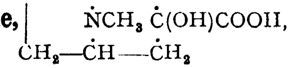
On oxidation with CrO_3, *l*- and *d*-ecgonine yield *l*-**ecgoninic acid,** *N*-**methylpyrrolidone-α-acetic acid,**



$$CH_2\begin{cases}CO - NCH_3 \\ CH_2 - CHCH_2COOH\end{cases}$$

m.p. 117°, whose racemic form, melting at 94°, also results from tropine with CrO_3, besides tropinic acid, and is obtained synthetically from β-bromadipic acid with methylamine (B. **34,** 1818). For further disintegration products see below.

α-Ecgonine,



melting at 305°, is a position isomeride of ecgonine. It has been prepared by adding hydrocyanic acid to tropinone, and then saponifying the cyanohydrin (B. **29,** 2216).

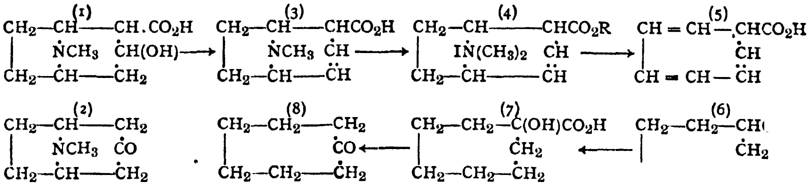
Anhydroecgonine, $C_9H_{13}NO_2$ (see below), melting at 234°, is produced on boiling ecgonine hydrochloride with phosphorus oxychloride (B. **20,** 1221). On reduction it is converted into **hydroecgonidine,** $C_9H_{15}NO_2$, m.p. 200°.

The connection or relation of ecgonine to tropine follows as a consequence of the rearrangement of anhydroecgonine (observed by Einhorn), upon heating with hydrochloric acid to 280°, into tropidine, carbon dioxide being eliminated (B. **23,** 1338).

The transition into tropidine is also obtained by the conversion of hydroecgonidine amide, $(C_8H_{14}N)CONH_2$, with KOBr into *iso*-**tropylamine,** $(C_8H_{14}N)NH_2$, which, on treatment with HNO_2, yields tropidine (B. **31,** 2655).

Disintegration and Synthesis of Ecgonine—Conversion of Ecgonine into Tropinone and Suberone.—The position of the carboxyl group in the tropine ring of ecgonine (1) is indicated by the oxidation to tropinone (2) with chromic acid. The accompanying elimination of CO_2 lends probability to the interpretation of ecgonine as a β-hydroxy-acid (B. **31,** 2655).

On converting anhydroecgonine (3) into the ester and treating it with methyl iodide, we obtain anhydroecgonine ester iodomethylate (4), which is converted by moist silver oxide into anhydroecgonine methyl betaïne. On boiling with alkali, this splits up into dimethylamine and tropilidene carboxylic acid or δ-*cyclo*heptatriene carboxylic acid (5), melting at 32° (amide at 125°). The constitution of the latter has been proved by its reduction to suberane carboxylic acid (6), and the conversion of the latter by way of bromo- or hydroxy-suberane carboxylic acid (7) into suberone (8) (Willstätter, B. **31,** 2498):



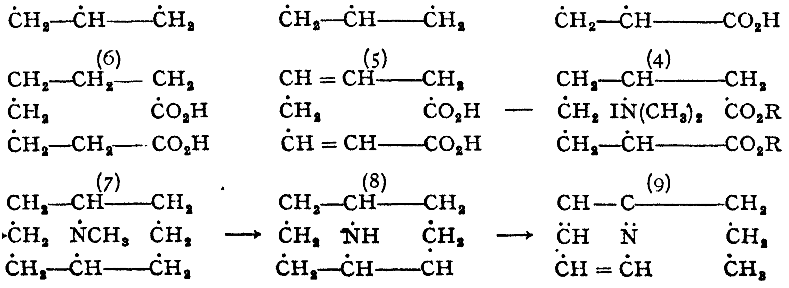
Like anhydroecgonine, the hydroecgonidine has been split up to form hydro-tropilidene carboxylic acid, or *cyclo*-heptadiene carboxylic acid (B. **30,** 702; **31,** 2501).

The conversion of ecgonine (1) into tropinone (2), which makes another bridge between cocaïne and atropine, is paralleled by a synthesis of ecgonine from tropinone; tropinone, synthesized from tropine, is partly reconverted into *racemic ecgonine* by treating with Na and CO_2 (B. **34,** 1457).

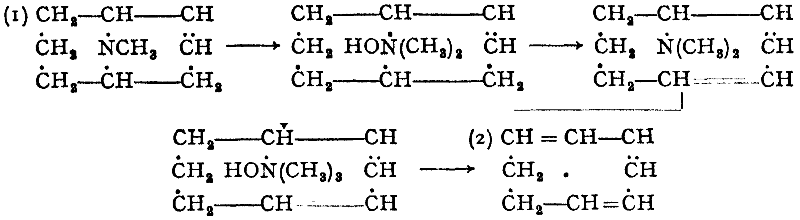
Pelletierine, $C_9H_{15}NO$, *iso*-, **methyl-,** and *pseudo***pelletierine** (named after the chemist Pelletier), were discovered by Tanret in *Punica granatum*. *pseudo*Pelletierine alone has been closely studied by Ciamician and Silber. They recognized this base as a near relative of the tropine series.

*pseudo***Pelletierine,** *methyl granatonine* (1), m.p. 48°, b.p. 246°, is a ring homologue of tropinone; like this, it forms a dibenzal and a di-*iso*-nitroso compound, and therefore contains the group $—CH_2.CO.CH_2—$ (C. 1899, I. 1292). By reduction it yields the alkamine ψ-methylgranatoline (2), corresponding to ψ-tropine (electrolytic reduction simultaneously produces the stereo-isomeric methyl granatoline). The ψ-methylgranatoline is oxidized by chromic acid to *pseudo*pelletierine, and further to methyl granatic acid (3), which corresponds to tropinic acid. Methyl granatic acid (3) has been disintegrated by the iodo-methylate method to suberic acid (6); methyl granatic acid ester iodo-methylate (4) is split up by alkali to dimethyl granatic acid, whose iodo-methylate, treated with alkali, gives homo-piperylenic acid (5), and this, on reduction with sodium amalgam, gives suberic acid (6).

On the other hand, methyl granatoline, reduced with HI and phosphorus, yields methyl granatanine (7) and granatanine (8) (see also B. **38,** 1896); the granatanine hydrochloride, by Zn dust distillation, yields *a-propylpyridine* (9) or conyrine:



By elimination of water with glacial acetic acid and concentrated H_2SO_4, methylgranatoline gives methylgranatanine (1), which, by analogy with tropidine and *cyclo*-heptatriene, has been split up into *cyclo*-octatriene (2) by exhaustive methylation:



Similarly, methylgranatanine yields $\Delta^{1,5}$-*cyclo*-octadiene; under somewhat different conditions methylgranatanine yields *granatal*, $C_8H_{12}O$, corresponding to tropilene, or Δ^3-*cyclo*-octenone (B. **29,** 481; **38,** 1975; **44,** 3423; C. 1899, II. 808, 828; 1900, I. 140).

CINCHONINE GROUP.

Cinchona Bases.—*Cinchona barks* (cortex chinæ) are derived chiefly from the various Cinchona species: *Cinchona Calisaya, C. lancifolia, C. Pitayensis,* etc.; also from the *Rubiaceæ.* They contain, in addition to tannin and *quinic acid* (II. 474), a series of bases, the most importan of which are:

Quinine, $C_{20}H_{24},N_2O_2$.	Conquinine (quinidine), $C_{20}H_{24}N_2O_2$.
Cinchonine, $C_{19}H_{22}N_2O$.	Cinchonidine, $C_{19}H_{22}N_2O$.

As companion substances to cinchonine we may also mention hydrocinchonine or cinchotine, $C_{19}H_{24}N_2O$ (A. **300,** 42; M. **20,** 425).

Quinine, $CH_3O.C_9H_5N.C_{10}H_{15}(OH)N+3H_2O$, melts, when anhydrous, at 177°. It consists of silky needles when crystallized from alcohol and ether. Pelletier and Caventou discovered quinine in 1820. It is one of our most valued medicines, especially for intermittent fevers —*e.g.*, malaria, etc.—and is an antidote for many infections produced by micro-organisms.[*]

It is found up to 12 per cent. in the yellow *Calisaya bark,* has an alkaline reaction and a bitter taste, and forms primary and secondary salts, being a di-acid base.

The neutral *sulphate,* $(C_{20}H_{24}N_2O_2)H_2SO_4+8H_2O$, and the mono-*hydrochloride,* $C_{20}H_{24}N_2O_2.HCl+2H_2O$, are employed in medicine. The former consists of long, shining needles, which fall to a white powder on exposure. It dissolves readily in dilute sulphuric acid, the solution exhibiting a beautiful blue fluorescence.

When chlorine water and then ammonia are added to the solution of quinine salt, there is produced a green precipitate, dissolving in an excess of ammonium hydroxide with an emerald-green colour. On adding an alcoholic iodine solution to the sulphate in acetic acid, a

[*] "Grundzüge der Arzneimittellehre," by C. Binz, 14th ed., 1912.

periodide, $4B.3SO_4H_2.2HI.I_4+6H_2O$, called *herapathite*, is precipitated. This crystallizes in emerald-green plates with golden lustre, and polarizes light like tourmaline.

Cinchonine, $C_9H_6N.C_9H_{12}(OH)(CH_3)N$, is associated with quinine, and occurs principally in the grey cinchona bark (*Cinchona Huanaco*) (upward of 2·5 per cent.). It crystallizes from alcohol in white prisms, sublimes in needles in a current of hydrogen, and melts at 255°. Like quinine, it seems to dissipate fever, but to a less degree.

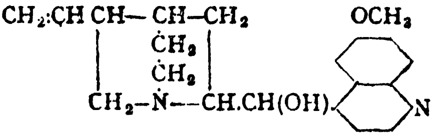
Quinidine, m.p. 171°, and *cinchonidine*, m.p. 201°, are shown by their reactions to be stereo-isomerides of quinine and cinchonine respectively. Accordingly, cinchonine can be converted into cinchonidine by heating with amyl alcoholic potash (B. **29**, 2185). On the stereo-chemistry of the cinchona alkaloids, see A. **373**, 85.

Quinine and cinchonine are unsaturated di-tertiary bases. They yield primary and secondary salts, and combine with 1 or 2 molecules alkyl iodide to form mono- and di-iodo-alkylates. The mono-iodo-alkylates are known in two isomeric forms, one of which is colourless, while the other has a dark yellow colour. The former result from the combination of the free bases with 1 molecule alkyl iodide, the latter from heating the mono-iodo-hydrates with alkyl iodide and subsequent treatment with ammonia (B. **26**, 1968).

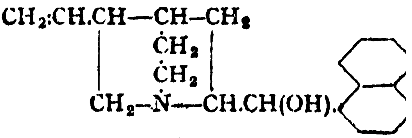
In accordance with their unsaturated nature, quinine and cinchonine combine with 1 molecule halogen hydride and 2 atoms of bromine. With alkali, the dibromides yield *mono-bromo-quinine* and *-cinchonine*, and further *dehydro-quinine* and *-cinchonine*, $C_{20}H_{22}N_2O_2$ and $C_{19}H_{20}N_2O$ respectively (B. **19**, 2856; J. pr. Ch. [2], **69**, 193). On the attachment of sulphurous acid to quinine and quinidine, see B. **35**, 2980. Reduction with hydrogen and colloidal palladium converts quinine, quinidine, cinchonine, and cinchonidine into the more hydrogenated bases—*hydroquinine*, *hydroquinidine*, *hydrocinchonine* (cinchotine), and *hydrocinchonidine* (cinchamidine). These contain two additional H-atoms, and have been found accompanying quinine and cinchonine in cinchona bark (B. **44**, 2866; C. 1911, I. 1567).

Strong mineral acids convert the cinchona alkaloids into various isomeric bases: iso*quinine*, iso*quinidine*, iso*cinchonine*, and iso*cinchonidine*. Special interest attaches to the action of hydro-halogen acids upon cinchonine at ordinary temperatures. This leads to the simultaneous formation of hydro-halogen cinchonine and *a-iso*cinchonine. The speeds of free HCl, HBr, and HI are in the ratio 1 : 400 : 20,000 (M. **20**, 571, 585; **22**, 171, 253; C. 1911, II. 1814).

On the basis of the researches of Koenigs, v. Miller, Rabe, Rhode, Skraup, and others, the following constitutional formulæ for quinine and cinchonine may be regarded as firmly established:



Quinine.

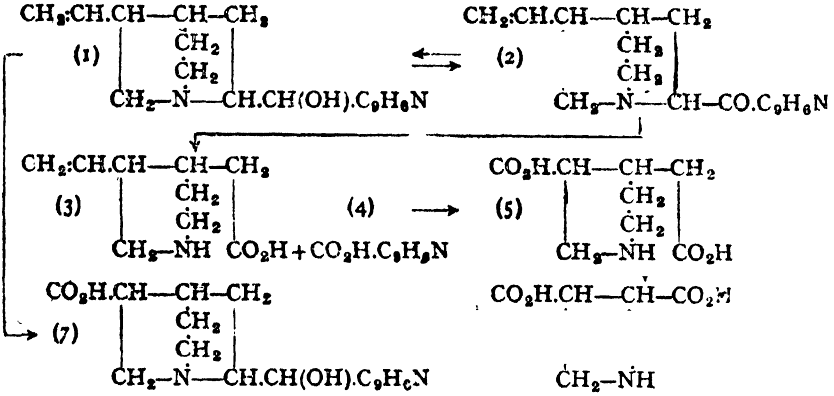


Cinchonine.

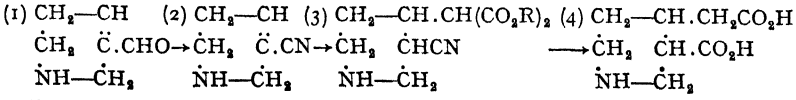
Quinine must therefore be regarded as methoxy-cinchonine. On heating with HCl to 150° the methyl group of the quinine is split off, with formation of apoquinine, but there is a simultaneous transposition of the molecule. De-methylated quinine (hydroxycinchonine), $C_{19}H_{33}N_2O_2$, has been found in *China cuprea*, a bark derived from *Remija pedunculata*. It is termed *cupreïne*, and can be methylated into quinine.

Oxidative Decomposition of the Cinchona Bases.—Careful oxidation of cinchonine (1) with chromic acid yields the ketone corresponding to a secondary alcohol, and called cinchoninone (2) which, on reduction, reverts to cinchonine. Similarly, quinine yields quininone. The ketones derived from cinchonidine and quinidine are identical with cinchoninone and quininone. Strong oxidation with chromic acid splits up the molecule of cinchonine and quinine with formation of cinchoninic acid (quinoline-γ-carboxylic acid) (4) or quinic acid (methoxyquinoline-γ-carboxylic acid) and mero-quinene (3) (μέρος, a portion). The latter, on further oxidation with $KMnO_4$, passes into *cincholoiponic acid* (λοιπός, remaining), or piperidine-β-carboxylic-γ-acetic acid (5), and further into *loiponic acid* (6) or hexahydro-cinchomeronic acid.

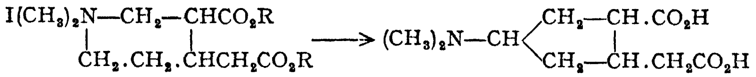
Dilute permanganate solution oxidizes cinchonine with evolution of formic acid and forms cinchotenine (7), while quinine forms quinotenine:



Synthesis of Cincholoiponic Acid.—This proceeds from Δ deïne-β-aldehyde (1) resulting from the hydrolysis of imino-dipropion acetal. The oxime of (1) is converted by means of $SOCl_2$ into Δ^β-piperideïne-β-nitrile (2). The ester nitrile (3), obtained from (2) by the attachment of sodium-malonic ester, yields, on saponification with baryta water, racemic cincholoiponic acid (4) in two stereoisomeric forms, the higher-melting of which yields on splitting up by means of brucine a *d*-cincholoiponic acid identical with the disintegration product of the cinchona bases (Wohl, B. **40,** 4698; **42,** 627):

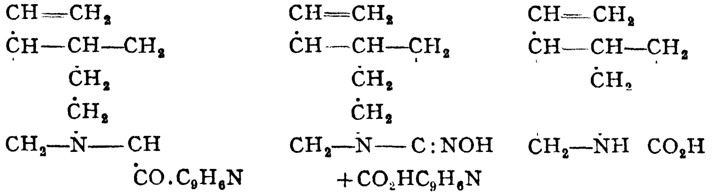


The iodo-methylate of cincholoiponic acid is converted by alkali into dimethyl-amino-*cyclo*pentanecarboxylicacetic acid (C. 1901, I. 223):



$$\begin{array}{l} I(CH_3)_2N{-}CH_2{-}CHCO_2R \\ \quad\;\; | \qquad\quad\;\; | \\ \quad CH_2.CH_2.CHCH_2CO_2R \end{array} \longrightarrow (CH_3)_2N{-}CH\begin{array}{l} \diagup CH_2{-}CH.CO_2H \\ \qquad\quad\;\; | \\ \diagdown CH_2{-}CH.CH_2CO_2H \end{array}$$

The above-mentioned cinchoninone, the first oxidation product of cinchonin, m.p. 127°, belongs to the tautomeric compounds. On the one hand, it yields, as a ketone, an oxime; on the other, it gives with acetyl- and benzoyl-chloride an acetyl- and benzoyl-compound derivable from the enol form. The action of amyl nitrite and sodium ethylate splits up cinchoninone, with formation of cinchoninic acid, and an *iso*-nitroso-compound which, as an interior amidoxime, yields, on saponification, hydroxylamine and mero-quinene (B. **41,** 62; A. **365,** 353):



$$\begin{array}{l} CH{=}CH_2 \\ CH{-}CH{-}CH_2 \\ \quad CH_2 \\ \quad CH_2 \\ CH_2{-}N{-}CH \\ \qquad\quad CO.C_9H_6N \end{array} \qquad \begin{array}{l} CH{=}CH_2 \\ CH{-}CH{-}CH_2 \\ \quad CH_2 \\ \quad CH_2 \\ CH_2{-}N{-}C{:}NOH \\ \quad +CO_2HC_9H_6N \end{array} \qquad \begin{array}{l} CH{=}CH_2 \\ CH{-}CH{-}CH_2 \\ \qquad CH_2 \\ \\ CH_2{-}NH \quad CO_2H \\ \end{array}$$

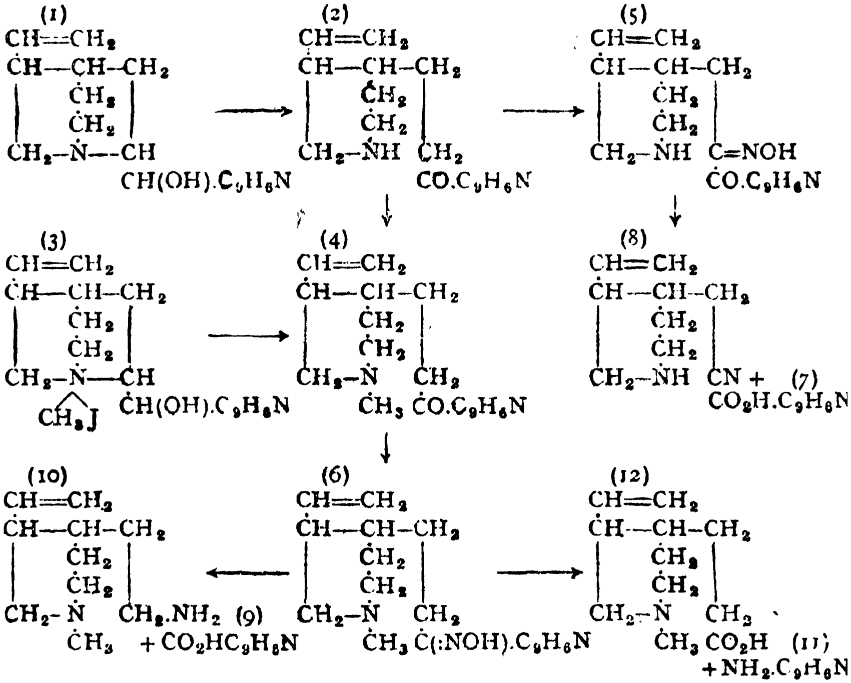
Disintegration of the Cinchona Bases—Quinatoxines.—The disintegration of the dicyclic "second half" of the cinchona bases, already noticed in their oxidation, occurs with remarkable facility in other reactions.

When cinchonine (1) and quinine are boiled with acetic acid, the union of that carbon atom to which hydroxyl is attached is severed from the nitrogen atom, which then becomes an imino-group, while the C(OH)-group becomes a keto-group. Cinchonine yields the isomeric *cinchotoxine* (2), melting at 59°, which, like the corresponding *quinotoxine*, is very poisonous, but does not have any antipyretic properties.

The "toxines" resulting from cinchonidine and quinidine are identical with those resulting from cinchonine and quinine. A similar disintegration is experienced by cinchonine iodo-methylate (3) on boiling with alkali or dilute acetic acid, HI being evolved, and *N*-methylcinchotoxine (4) formed, which can also be obtained by methylating cinchotoxine. The latter, with HNO_2, yields a mono-*iso*nitroso-compound. Remarkable results have been obtained by a Beckmann transposition of this *iso*-nitroso-cinchotoxine (5) and of the *N*-methylcinchotoxine oxime (6).

Iso-nitrosocinchotoxine splits up into cinchoninic acid (7) and the nitrile of mero-quinene (8). In (6) the transposition is in two directions, cinchoninic acid (9) and *N*-methyl-β-vinyl-γ-amino-ethylpiperidine (10) being formed on the one hand, and γ-amino-quinoline (11) and *N*-

methyl-homo-mero-quinene (12) on the other (B. **40**, 648, 2873; A. **382**, 365):

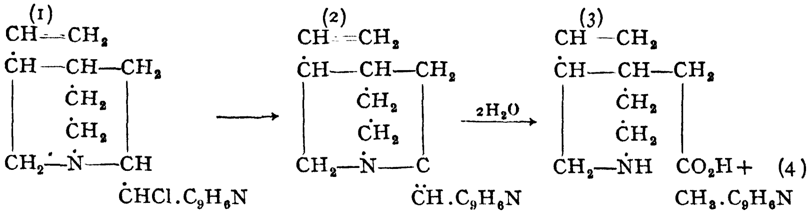


Cinchotoxine has been used for a partial synthesis of cinchonine. Under the influence of hypo-bromous acid it yields a bromimine from which sodium ethylate withdraws a molecule of HBr, forming cinchoquinone, which may, as already stated, be reduced to cinchonine (B. **44**, 2088). We may also mention the synthesis of quinuclidine, already dealt with, which corresponds to that of the second half of the cinchona bases.

Decomposition of Cinchonine and Quinidine Chloride (J. pr. Ch. [2], **61**, 1).—On treating cinchonine and quinine with PCl_5, cinchonine chloride (1) and quinine chloride are produced. These, when boiled with alcoholic potash, split off 1 molecule HCl and form cinchene (2) and quinene. Cinchonidine and quinidine, under the same treatment, also pass into cinchene and quinene respectively. The chlorides of the four alkaloids—viz., cinchonine, cinchonidine, quinine, and quinidine chloride—replace, on reduction, the chlorine atoms by hydrogen atoms, and give four desoxy compounds: *Desoxy-cinchonine, desoxy-cinchonidine, desoxy-quinine,* and *desoxy-quinidine.*

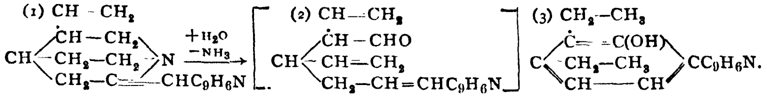
Cinchene and quinene are split up, with absorption of water, in two entirely different ways according to the experimental conditions.

On heating with 20 per cent. aqueous solution of phosphoric acid, cinchene and quinene split up into lepidine (4) or methoxy-lepidine and mero-quinene (3):



On prolonged boiling with HBr, cinchene and quinene split off ammonia and some methyl bromide, and take up water, forming apo-cinchene and apo-quinene, $C_{19}H_{20}N_2$ (Cinchene) + $H_2O = C_{19}H_{19}NO$ (Apo-cinchene) + NH_3. Decomposition and partial synthesis have proved apo-cinchene to be **γ[2-hydroxy-3,4-diethylphenyl]-quinoline.** Apo-quinene, accordingly, is **γ[2-hydroxy-3,4-diethylphenyl]-hydroxy-quinoline.**

An idea of the formation of apo-cinchene (3) by the hydrolysis of cinchene (1) may be gained from the following scheme, with the help of the cinchonine formula above:



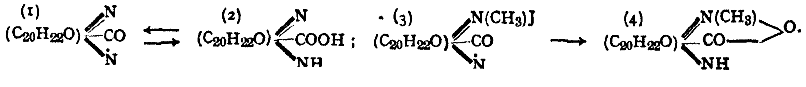
The transposition of the hypothetical intermediate product (2) into the phenylquinoline derivative finds an analogy in the transition of the olefinic terpenes into cyclic compounds, as in the conversion of citronellal into *iso*pulegol, etc.

Strychnos Bases.—In the fruit of the different strychnos, principally in that of *Strychnos nux vomica* and in St. Ignatius' bean (*Strychnos Ignatii*), are found two very poisonous bases, *strychnine* and *brucine*. Their constitution is imperfectly determined. They were discovered (1818 and 1819) by Pelletier and Caventou.

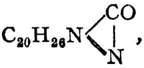
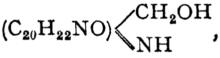
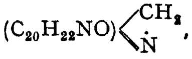
Strychnine, $C_{21}H_{22}N_2O_2$, melting at 284° and boiling at 270° (5 mm.) (B. **19**, R. 30), is lævorotatory, reacts alkaline, has an extremely bitter taste, and occasions tetanus.

Strychnine is an unsaturated mono-acid, tertiary amine base, capable of adding on alkyl halides (A. **304**, 49). The second N-atom is in lactam connection with one CO-group. This follows from the transformation of strychnine (1) by heating with sodium alcoholate solution into **strychnic acid** (2), $C_{21}H_{24}N_2O_3$, which, on boiling with acids, regenerates strychnine.

On treating strychnine iodo-methylate (3) with moist silver oxide, methylstrychnine (4) is formed, which turns out to be strychnic acid methyl betaïne, since it also results from the silver salt of strychnic acid iodo-methylate. There is therefore a change of linkage of the carboxyl group from one N-atom to the other, from the lactam linkage to the betaïne linkage:

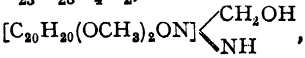
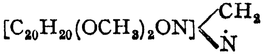


On heating with water to 160°–180°, strychnine passes into an isomeric base, *iso***strychnine,** m.p. 214°, which, like strychnine, is split up on heating with sodium alcoholate solution into an acid iso-*strychnic acid* (B. **38,** 2787).

Reduction of strychnine with hydrogen and colloidal palladium gives, as a first reduction product, **dihydrostrychnine,** $C_{21}H_{24}N_2O_2$ (B. **44,** 2863). With HI and phosphorus we obtain **desoxystrychnine,**  $C_{20}H_{26}N{<}\begin{smallmatrix}CO\\ |\\ N\end{smallmatrix}$, which is still a lactam, and yields by electrolysis **tetrahydrostrychnine,**  $(C_{20}H_{22}NO){<}\begin{smallmatrix}CH_2OH\\ NH\end{smallmatrix}$, and **strychnidine,**  $(C_{20}H_{22}NO){<}\begin{smallmatrix}CH_2\\ \dot{N}\end{smallmatrix}$, which involves a reduction of the lactam group. A further reduction eliminates the second O-atom, whose function is not yet clear. The results are **dihydro-strychnoline,** $C_{21}H_{28}N_2$, and **strychnoline,** $C_{21}H_{26}N_2$.

Transformation products of strychnine which no longer contain the lactam ring recall in their behaviour the tetrahydroquinolines. By the action of nitric acid, several nitro-derivatives have been obtained from strychnine; also picric acid and an acid which is regarded as *dinitrodihydroxyquinoline* (A. **301,** 285). On oxidation with $KMnO_4$ in acetone solution strychnine forms strychninonic acid, $C_{21}H_{20}O_6N_2$, a dibasic ketonic acid, converted by sodium amalgam into the corresponding hydroxy-acid, **strychninolic acid,** $C_{21}H_{22}O_6N_2$. The latter, under the influence of dilute alkali, even in the cold, splits up into glycolic acid, and the **neutral strychninolone,** $C_{19}H_{18}O_3N_2$ (B. **43,** 2417). Heated with H_2O_2, strychnine forms **strychnine oxide,** $C_{21}H_{22}N_2O_3$, and **strychnine peroxide,** $C_{21}H_{22}N_2O_4$, which regenerate strychnine with evolution of oxygen (B. **38,** 2782; C. 1910, II. 887). By the action of MnO_2 and sulphurous acid, strychnine forms three isomeric strychnine monosulphonic acids, $C_{21}H_{21}O_2N_2(SO_3H)$, which can be separated by their different solubilities in water (B. **42,** 2681).

Brucine, $C_{21}H_{20}(OCH_3)_2N_2O_2+4H_2O$, m.p. 178° (anhydrous), lævorotatory, acts similarly to strychnine, but more feebly. In its chemical reactions it behaves very like strychnine. It contains two methoxyl groups, and is probably dimethyoxy-strychnine. Sodium alcoholate converts it into **brucic acid,** $C_{20}H_{21}(OCH_3)N_2O(COOH)$, which regenerates brucin on merely boiling with water.

Hydrogen and colloidal palladium convert it into dihydro-brucine, $C_{23}H_{28}O_4N_2$, and electrolytic reduction into **tetrahydro-brucine,**  $[C_{20}H_{20}(OCH_3)_2ON]{<}\begin{smallmatrix}CH_2OH\\ NH\end{smallmatrix}$, and **brucidine,**  $[C_{20}H_{20}(OCH_3)_2ON]{<}\begin{smallmatrix}CH_2\\ \dot{N}\end{smallmatrix}$ (A. **304,** 24).

Potassium permanganate oxidizes brucine to **brucinonic acid,** $C_{23}H_{24}O_8N_2$, which, in the manner of strychninonic acid, may be converted into **brucinolic acid,** $C_{23}H_{26}O_8N_2$, and **brucinolone,** $C_{21}H_{22}O_5N_2$ (B. **42,** 3703). Treated with H_2O_2, brucin gives **brucine oxide,** $C_{23}H_{26}N_2O_5$, and **brucine peroxide,** $C_{23}H_{26}N_2O_6$. With MnO_2 and sulphurous acid, four *isomeric brucine mono-sulphonic acids,* $C_{23}H_{25}N_2O_4(SO_3H)$, are formed (B. **44,** 3049). In concentrated nitric acid, brucine dissolves with a red colour, which, on heating, turns yellow, and on addition of stannous chloride into violet. In this case brucin is first demethylated and oxidized, forming a red quinone, $C_{21}H_{20}O_4N_2$, which, on further action of nitric acid, adds a nitro-group, and yields the yellow so-called **cacotheline,** $C_{21}H_{21}O_7N_3$. Reduction of quinone with sulphurous acid gives *demethylated brucine,* $C_{21}H_{20}(OH)_2N_2O_2$ (B. **44,** 2136, 3040). Brucinolone and the brucine sulphonic acids behave in the same manner towards nitric acid. On the constitutional formulæ of strychnine and brucine, see C. 1910, I. 1361.

The *veratrum alkaloids* occur, together with veratric acid, in the white hellebore (from *V. album*) and in the sabadilla seeds (from *V. sabadilla*). **Crystalline Veratrine** (B. **26,** R. 284), or **cevadine,** $C_{32}H_{49}NO_9$, melts at 202° and crystallizes from alcohol with 1 molecule crystal alcohol. It dissolves in concentrated sulphuric acid with a yellow colour, which gradually changes to blood-red.

Alcoholic potash splits it into **cevine,** $C_{27}H_{43}NO_8$, and *tiglic acid,* $C_5H_8O_2$ (see Vol. I.) (B. **32,** 800; C. 1902, I. 1155). Cevadine contains a free OH-group: $C_{27}H_{41}NO_6(OH)(O.COC_4H_7)$, and cevine contains two OH-groups, $C_{27}H_{41}NO_6(OH)_2$. The N-atom is probably linked in a tertiary manner (B. **37,** 1946).

THE MORPHINE AND ISOQUINOLINE GROUP OF THE VEGETABLE ALKALOIDS.

Opium Bases.—In opium, the dried juice of the green seed capsules of poppy (*Papaver somniferum*), we find not only meconic acid and meconine, but a series of bases, of which may be mentioned:

Morphine, $C_{17}H_{19}NO_3$ (12 %).
Codeïne, $C_{18}H_{21}NO_3$ (0·3 %).
Thebaïne, $C_{19}H_{21}NO_3$ (0·4 %).
Papaverine, $C_{20}H_{21}NO_4$ (0·8 %).
Narcotine, $C_{22}H_{23}NO_7$ (5 %).
Narceïne, $C_{23}H_{27}NO_8$ (0·2 %).
Laudanosine, $C_{21}H_{27}NO_4$ (0·0008

While the constitution of *papaverine, narcotine, narceïne,* and *laudanosine* is settled and confirmed by synthesis, the nature of the principal basis of opium, morphine, with its related substances, codeïne and thebaïne, is not yet known with certainty. They probably contain no *iso*quinoline ring, but are treated, however, with the other opium bases. Morphine is the most important of them from a medical point of view.

Morphine, $C_{17}H_{17}NO(OH)_2 + H_2O$, crystallizes from alcohol in small prisms, tastes bitter, and in small quantities produces sleep. It shows an alkaline reaction, and represents a tertiary monacid base. Its official hydrochloride, $C_{17}H_{19}NO_3HCl + 3H_2O$, forms delicate silky needles. It is used to relieve pain and to produce sleep. Morphine is the first alkaloid isolated from vegetable substances (Sertürner, 1806). Its composition was determined by Laurent in 1848.

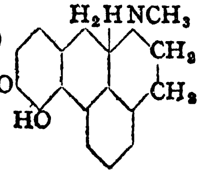
The solutions of morphine and its salts are coloured dark blue by ferric chloride; the solution in concentrated sulphuric acid acquires a blood-red coloration on the addition of a little nitric acid. It is readily oxidized, two molecules uniting, with the exit of two hydrogen atoms, to *pseudo***morphine,** $(C_{17}H_{18}NO_3)_2$ (A. **294,** 206).

In the reduction of morphine with hydrogen and colloidal palladium, dihydro-morphine, $C_{17}H_{21}O_3N$, is produced with addition of 2H (B. **44,** 2865). Morphine contains two hydroxyl groups and behaves like a phenol alcohol, yielding salts with but one metallic atom, but diacidyl derivatives. Diacetylmorphine is officially known as *heroïne.* On distillation with zinc dust, morphine yields phenanthrene with a mixture of two bases (B. **34,** 1162).

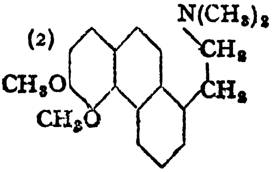
By treatment with phosphorus haloids, or by the action of anhydrous liquid halogen hydrides, the alcoholic hydroxyl in morphine is replaced by halogen, with formation of chloro-morphide, $C_{17}H_{17}Cl(OH)O$, and bromo-morphide, from which hydrolysis produces three bases isomeric with morphine—viz., α-, β-, and γ-*iso*-morphine (see codeïne) (B. **41,** 975).

By heating with concentrated HCl to 140°–150°, or by the action of other dehydrating agents, like sulphuric, phosphoric, and oxalic acids, morphine is deprived of 1 molecule H_2O and converted into **Apo-morphine,** $C_{17}H_{17}NO_2$ (1). This is quite different from morphine in its physiological properties. It is no longer a narcotic, but a strong emetic. Its bromo-methylate is used medicinally under the name *euporphine.* In contrast with morphine, apomorphine contains two phenol hydroxyls. Its dimethyl ether can be disintegrated by the splitting of its iodo-methylate by Hofmann's method, forming *dimethyl apo-morphimethine* (2) and 3,4-*dimethoxy*-8-*vinylphenanthrene,* and the latter by oxidation to 3,4-*dimethoxyphenanthrene*-8-*carboxylic acid* (3) (B. **40,** 1984). Since the attachment of the nitrogen atom is known from the connection between morphine and codeïne (see oxycodeïne), the constitution of apo-morphine may be regarded as determined:

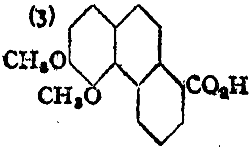
(1)



(2)

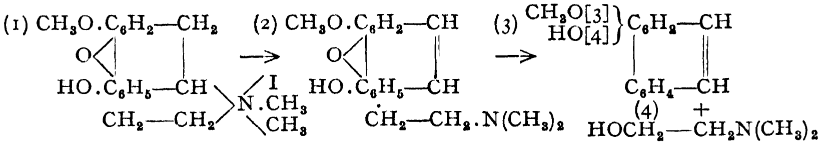


(3)

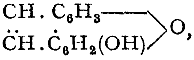


From a comparison with the similar transformation of thebaïne into morphothebaïne and thebenine (see below), it follows that the transition of morphine to apo-morphine is attended by an extensive transposition, so that no conclusion respecting the structure of morphine can be based upon the constitution of apo-morphine.

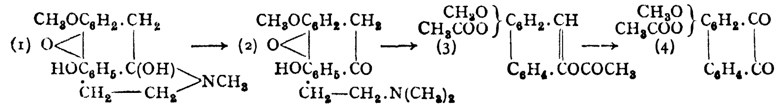
Codeïne, $C_{17}H_{17}NO(OCH_3)OH$, m.p. 150°, is contained in opium, and can be obtained from morphine by methylating with KHO and methyl iodide or dimethyl sulphate, or by means of diazo-methane, and must therefore be regarded as methyl-morphine (B. **14,** 1413; C. 1899, II. 408). Its iodo-methylate (1), on heating with alkali, furnishes the so-called **α-methylmorphimethine** (2), m.p. 118°. This, on heating with acetic anhydride, splits up into the acetyl esters of hydroxyethyldimethylamine (4) and of *methylmorphol* or 4-*oxy*-3-*methoxyphenanthrene* (3) (B. **37,** 3494):



The constitution of the morphol or 3,4-dihydroxyphenanthrene is proved by its oxidation to morpholquinone (dihydroxyphenanthrenequinone), and further to phthalic acid, as well as the synthesis of dimethylmorphol (3,4-dimethoxy-phenanthrene) from 2,3,4-amino-dimethoxy-α-phenyl cinnamic acid (B. **33,** 1810, 1824).

On the other hand, the splitting up of the iodo-methylate of methyl morphimethine by alcoholic alkali produces tri-methylamine and **Morphenol,**  $\begin{array}{l}CH.C_6H_3\text{——}\\ CH.C_6H_2(OH)\end{array}\!>\!O$, a phenanthrene derivative resembling diphenylene oxide (B. **33,** 352; **34,** 2722).

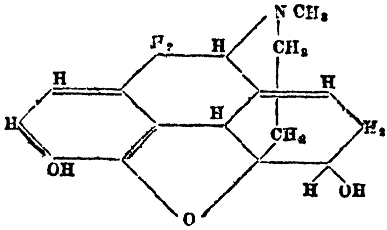
Careful oxidation with chromic acid converts codeïne into **oxycodeïne,** $C_{17}H_{16}NO(OCH_3)(OH)_2$ (1). This contains two alcoholic hydroxyl groups and, like codeïne, produces oxy-methyl morphimethine (2) by disintegration of its iodo-methylate. The body thus produced has ketonic properties. On heating with acetic anhydride it splits up into acetoxyethyl-dimethylamine and *methoxydiacetoxyphenanthrene* (3), which, on oxidation, passes into *methyl-acetyl-morpholquinone* (4):



Hence it follows (1) that the newly-acquired hydroxyl is attached to one of the linking carbon atoms of the phenanthrene nucleus (9 or 10); (2) from the alcoholic function of this hydroxyl group, that the phenanthrene bridge in the morphine alkaloids is hydrogenated; (3) from the transformation of a hydroxyl group into a carbonyl group on the passage of oxycodeïne into oxymethyl-morphimethine, that *in the morphine alkaloids the nitrogen of the side ring is linked to the hydrogenated bridge of the phenanthrene nucleus* (B. **40,** 1980, 2042).

By permanganate in acetone solution, or by hot chromic acid mixture, codeïne is oxidized to **codeinone,** $C_{18}H_{10}NO_3$, the oxime-forming ketone group of which is formed from the alcoholic OH-group of morphine (see above). In contrast with codeïne, and by analogy with thebaïne, codeïnone is directly split by boiling with acetic anhydride into hydroxyethylmethylamine and 3-*methoxy*-4,6-*dioxy-phenanthrene*.

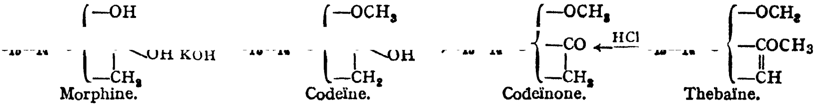
Phosphorus haloids, by replacing the alcoholic hydroxyl by halogen, convert codeïne into **chloro-codide,** $C_{17}H_{17}Cl(OCH_3)O$, and bromo-codide, as in the case of morphine. Hydrolysis does not regenerate codeïne from these, but produces, according to the conditions, three isomers of codeïne, called *iso*codeïne, *pseudo*-codeïne, and *allo-pseudo*-codeïne respectively. Of these, *iso*codeïne is stereo-isomeric with codeïne, since oxidation with CrO_3 produces the same codeïnone (see above). Similarly, *pseudo*-codeïne and *allo-pseudo*-codeïne are structurally identical, but yield on oxidation a *pseudo*-codeïnone isomeric with codeïnone, whose iodo-methylate, on boiling with alcohol, is disintegrated to form 3-methoxy-4,8-dioxy-phenanthrene. The conversion of codeïne into *pseudo*-codeïne and *allo-pseudo*-codeïne is therefore accompanied by a displacement of the alcohol hydroxyl from position 6 to position 8. Since the replacement of the OH-group by H results in the production of the same desoxy-codeïne, $C_{18}H_{21}NO_2$, from all isomeric forms of codeïne, thus indicating an identical C,N-skeleton, the position 8 cannot be contemplated for the attachment of the nitrogen ring to the phenanthrene nucleus in the morphine alkaloids. Position 7 is also excluded by the presence of a CH_2 group in codeïnone and *pseudo*-codeïnone, capable of reaction, and adjoining the carbonyl. These facts, in conjunction with the transformations of thebenine described below, have led to the establishment of the " bridge formula " for morphine (Knorr, B. **40,** 3341):



Fusion of codeïne, or, better, of *pseudo*-codeïne, with oxalic acid produces *pseudo*-**apo-codeïne,** $C_{18}H_{19}NO_2$, the 3-methyl ethyl of apomorphine (B. **41,** 3050).

Thebaïne, $C_{17}H_{15}NO(OCH_3)_2$, silvery plates, m.p. 193°, is closely related to codeïnone, into which it passes on saponification with dilute mineral acids, with elimination of a methyl group. Thebaïne thus turns out to be the methyl ether of the enol form of codeïnone.

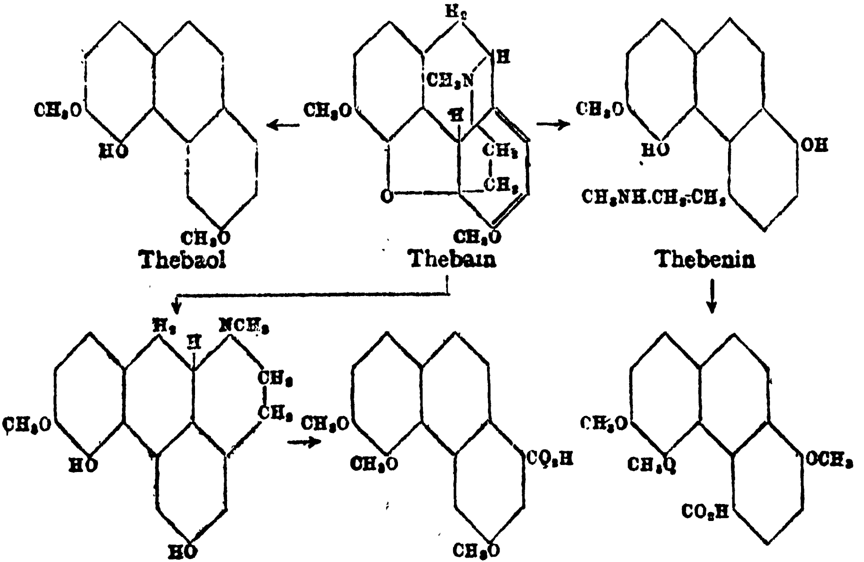
The connection between the three morphine alkaloids—morphine, codeïne, and thebaïne—can be represented by the following scheme (B. **39,** 1409):



Boiling with acetic anhydride splits up thebaïne into the acetyl esters of hydroxyethylmethylamine and of 3,6-dimethoxy-4-oxyphenanthrene, or *thebaol.* The latter has been synthesized from 2-amino-3,4-dimethoxy-α-(p-methoxy-phenyl-)-cinnamic acid (see phenanthrene syntheses) (B. **35,** 4400).

By heating with HCl thebaïne is transformed in two different ways, according to the concentration of the acid. When heated for a short time with dilute acid, a secondary base is produced, called *thebenine,* $C_{17}H_{14}N(OH)_2(OCH_3)$, while concentrated HCl produces a tertiary base, *morpho-thebaïne*, $C_{17}H_{14}N(OH)_2(OCH_3)$. In both cases, codeïnone is primarily formed, which in the same reaction conditions also passes into thebenine and morpho-thebaïne respectively. Morpho-thebaïne is an analogue of apo-morphine. Its dimethyl ether can be disintegrated by Hofmann's method to 3,4,6-*trimethoxy*-8-*vinyl-phenanthrene*, and this, by oxidation, to 3,4,6-*trimethoxy-phenanthrene*-8-*carboxylic-acid* (A. **373,** 52; **382,** 50). On the other hand, the di-methyl ether of thebenin yields by a similar process 3,4,8-*trimethoxy-phenanthrene*-5-*carboxylic acid.*

The nitrogenated side chain therefore probably attaches to the C-atom (5) of the phenanthrene nucleus in thebenine, and probably also in the three morphine alkaloids—morphine, codeïne, and thebaïne. This agrees with the fact that **Thebenol,** $(CH_3O)(HO)C_{14}H_6\left\{\begin{array}{l}CH_2\\O\end{array}\right\rangle O$, obtained from thebenine by treatment with methyl iodide and subsequent decomposition with KHO, yields pyrene by zinc-dust distillation (B. **43,** 2128). Thebenine also yields pyrene on zinc-dust distillation, as well as the base **thebenidine,** $C_{14}H_9N$, which resembles phenanthridine (B. **34,** 767). In the formation of thebenine the displacement of the OH-group from position 6 to position 8 is to be noted, as in the transition from codeïne to *pseudo*-codeïne. This is confirmed by the formation of triacetylthebenine on heating *pseudo*-codeïnone with acetic anhydride (A. **373,** 56). The following table gives the chief transformations of thebaïn:

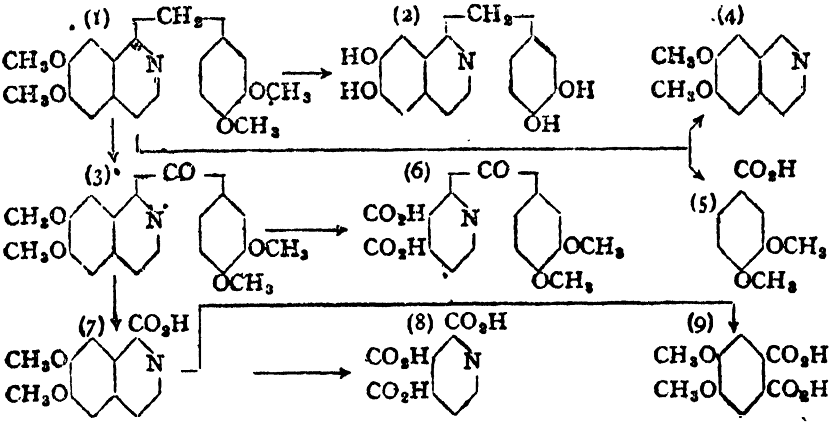


Morpho-thebaïne.

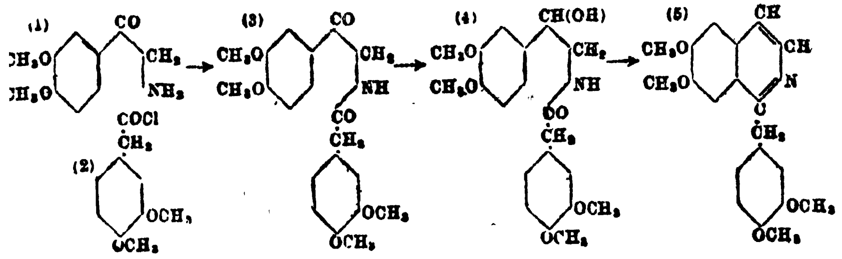
3,4,6-Trimethoxyphenanthrene-8-carboxylic Acid.

3,4,8-Trimethoxyphenanthrene-5-carboxylic Acid.

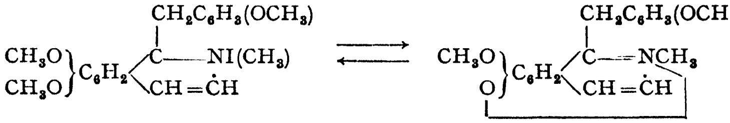
Papaverine (1), *tetramethoxy-benzyl*iso*quinoline*, $C_{20}H_{21}NO_4$, m.p. 148°. Its constitution results from its disintegrations. HI splits off $4CH_3I$, producing papaveroline (2). $KMnO_4$ converts papaverine into papaveraldine (3) or tetramethoxy-benzoyl*iso*-quinoline, which is also found in opium (C. 1911, I. 987). Fusion with KOH splits up papaverine into dimethoxy*iso*quinoline (4) and veratric acid (5). The oxidation of papaveraldine produces papaveric acid, α-dimethoxy-benzoyl-pyridine-βγ-dicarboxylic acid (6), dimethoxy-*iso*quinoline-carboxylic acid (7), αβγ-pyridine-tricarboxylic acid (8), and meta-hemipinic acid (9) (G. Goldschmidt, B. **21**, R. 650). In the following scheme the H-atoms attached to the rings are omitted for the sake of clearness:



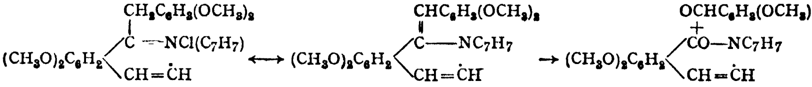
Synthesis of Papaverine (A. Pictet, B. **42**, 2943).—The *iso*-nitroso-compound produced from aceto-veratrone with amyl nitrite and sodium ethylate is reduced by means of stannous chloride and HCl to ω-amino-aceto-veratrone (1). This condenses with homo-veratric acid chloride (2) in the presence of alkali to form homo-veratroyl-ω-amino-aceto-veratrone (3), which is reduced by sodium amalgam to ***homo-veratroyl-hydroxyhomoveratrylamine*** (4). The latter, treated with P_2O_5 in boiling xylene solution (compare *iso*quinoline syntheses), splits off $2H_2O$ and forms *papaverine* (5):

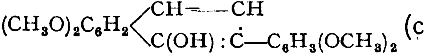


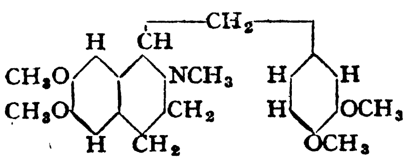
Of other transformations of papaverine we may mention those of the papaverine halogen alkylates. On treatment with *dilute* alkalies they yield, with saponification of one methoxyl group of the *iso*-quinoline nucleus, phenolbetaïnes, from which the papaverine iodalkylates are regenerated by heating with methyl iodide (A. **358,** 288):



By the action of *concentrated* alkali the halogen alkylates of papaverine split off halogen hydrides, and are converted into *N*-alkyl-*iso*-papaverines, which, with acids, regenerate the quaternary salts, and are split up by oxidation into *N*-alkyl*iso*quinolones and vanillin methyl-ether (B. **37,** 520)—*e.g.*:



Finally, on heating with alcoholic potash, papaverine iodo-methylate splits off methylamine and is converted into **tetramethoxy-β-phenyl-α-naphthol,**  $(CH_3O)_2C_6H_2<\begin{matrix}CH=CH\\C(OH):\dot{C}—C_6H_3(OCH_3)_2\end{matrix}$ (compare the transition from α-benzyl*iso*quinoline iodo-methylate to β-phenyl-α-naphthol) (A. **362,** 305):

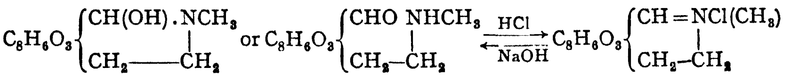


Laudanosin

Laudanosine, $C_{21}H_{27}NO_4$, m.p. 115°, is found in opium in very small quantities (about 0·0008 per cent.). It is closely related to papaverine, whose methochloride passes, on reduction with tin and HCl, into the hydro-chloride of [*d* + *l*]-laudanosine, which must therefore be regarded as *N-methyl-tetrahydro-papaverine*. The [*d* + *l*]-laudanosine can be split up by means of its quinate into its optically active antipodes, the dextro-rotatory modification being identical with the laudanosine found in opium. The synthesis of papaverine therefore includes that of laudanosine. On a further synthesis, by way of dihydropapaverine, see B. **42,** 1979.

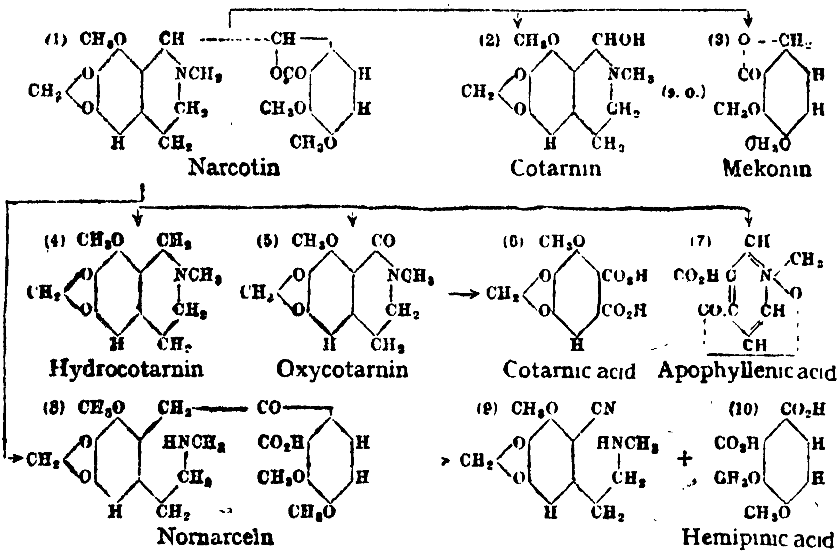
Narcotine (1), $C_{22}H_{23}NO_7$, m.p. 176°, $[\alpha]\gamma = 207{\cdot}35°$, is separated from morphine by means of KHO, in which it is insoluble (Robiquet, 1817). On heating with alcohol or acetic acid it is racemized to **gnoscopine** = [*d* + *l*]-narcotine, m.p. 233°, which is also found among the opium alkaloids, but is probably a secondary body derived from narcotine. Through its *d*-bromo-campho-sulphonate it can be split up into *d*- and *l*-narcotine (C. 1911, I. 1861; B. **44,** 800). Heated in water to 140°, narcotine is split up into **cotarnine** (2), $C_{12}H_{15}NO_4$, m.p. 125° (Wöhler, 1844, A. **50,** 1) and meconine (3); the latter, by oxidation, passes into opianic and hemipinic acids.

Cotarnine is a "pseudo-ammonium base" of the *iso*-quinoline series, from which acids generate the salts of the real isomeric ammonium base. As for these *pseudo*-bases, so also for cotarnine, the desmotropic formula of a secondary amino-aldehyde must be considered (B. **33,** 2273; C. 1904, II. 455):



$$C_8H_6O_3\left\{\begin{array}{l}CH(OH).NCH_3\\ \quad\quad\quad |\\ CH_2\text{——}CH_2\end{array}\right. \text{or } C_8H_6O_3\left\{\begin{array}{l}CHO\ NHCH_3\\ \quad |\\ CH_2-CH_2\end{array}\right. \underset{NaOH}{\overset{HCl}{\rightleftarrows}} C_8H_6O_3\left\{\begin{array}{l}CH=NCl(CH_3)\\ \quad |\\ CH_2-CH_2\end{array}\right.$$

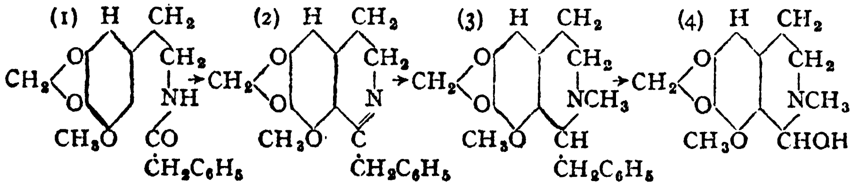
This tautomeric character of cotarnine explains some of its rather contradictory reactions. Thus, cotarnine as an aldehyde yields, with hydroxylamine, a cotarnine oxime (A. **254,** 335); with aniline it gives cotarnine anil, which, with cold methyl iodide, gives a quaternary trimethyl ammonium iodide, $C_8H_6O_3\left\{\begin{array}{l}CH:NC_6H_5\\ C_2H_4N(CH_3)_3I\end{array}\right.$ (B. **36,** 1522). With ketones, and substances with a methylene group capable of reaction, cotarnine also condenses with elimination of water, forming compounds, to some of which the open formula can be proved to apply by the preparation of a benzoyl derivative. This is the case in anhydro-cotarnineacetone, $C_8H_6O_3\left\{\begin{array}{l}CH:CHCOCH_3\\ CH_2.CH_2NHCH_3\end{array}\right.$ (B. **37,** 2744). On the other hand, on reduction (compare B. **31,** 1577) cotarnine yields hydro-cotarnine (4), and on oxidation with $KMnO_4$, oxy-cotarnin (5) (C. 1900, I. 1029; B. **35,** 1737), both of which must be regarded as true tetrahydro*iso*quinoline derivatives. On further oxidation oxy-cotarnine becomes cotarnic acid (6), a methoxymethylenedioxybenzene dicarboxylic acid, which, on heating with HCl, yields methyl methylene gallic acid and with HI gallic acid (W. Roser, A. **249,** 156; **254,** 334; **272,** 221; synthesis of cotarnic acid, see C. 1910, I. 542). Nitric



acid oxidizes cotarnine to apo-phyllenic acid (7), the methyl betaïne of cinchomeronic acid (compare B. **29,** 2190). On boiling with dilute acetic acid, narcotine, like the cinchona alkaloids, is split up to form a ketone—viz., *nornarceïne* (8)—whose *iso*nitroso-compound in Beckmann's transposition splits up into hemipinic acid (10) and a nitrile (9) (A. **377,** 223) (for diagram, see p. 253).

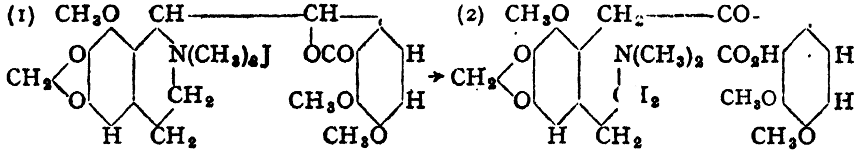
The position of the CH_3O- and CH_2O_2-groups in the *iso*quinoline nucleus of narcotine, cotarnine, etc., is proved as follows: As *o*-methoxybenzaldehyde anil, in contrast with the *m*- and *p*-derivatives, is split up by methyl iodide into methyl-aniline and *o*-hydroxybenzaldehyde, so also does cotarnine anil (see above), treated with warm methyl iodide, pass into a hydroxyaldehyde (B. **36,** 1523), a proof of the ortho-situation of the CH_3O- and CHO-groups in cotarnine. On the action of magnesium-organic compounds upon cotarnine, see B. **44,** 2353.

Synthesis of Cotarnine and Narcotine.—**3-Methoxy-4,5-methylene-dioxy-phenyl-propionic-acid,** $CH_3O[3]CH_2O_2[4,5]C_6H_2[1]CH_2.CH_2CO_2H$, obtained from *myristicin aldehyde,* $CH_3O[3]CH_2O_2[4,5]C_6H_2[1]CHO$, by condensation with acetic ester, saponification, and reduction, is converted, by treating its amide with hypochlorite, into *homo-myristicylamine,* $CH_3O[3]CH_2O_2[4,5]C_6H_2[1]CH_2.CH_2NH_2$. The phenacetyl compound of this base (1) condenses, on heating with P_2O_5 in xylene, to form 1-methoxy-2,3-methylenedioxy-α-benzyl-dihydro*iso*quinoline (2), whose iodo-methylate is reduced by tin and HCl to α-benzyl-hydrocotarnine (3). The latter is oxidized by manganese dioxide and dilute sulphuric acid to cotarnine (4) with elimination of benzaldehyde (C. 1910, II. 478; compare also C. 1911, II. 1267, 1816):



Cotarnine and meconine combine on boiling in methyl alcohol solution to form [*d* + *l*]-narcotine or gnoscopine, which, as already mentioned, can be split up into *d*- and *l*-narcotine (C. 1911, I. 1861).

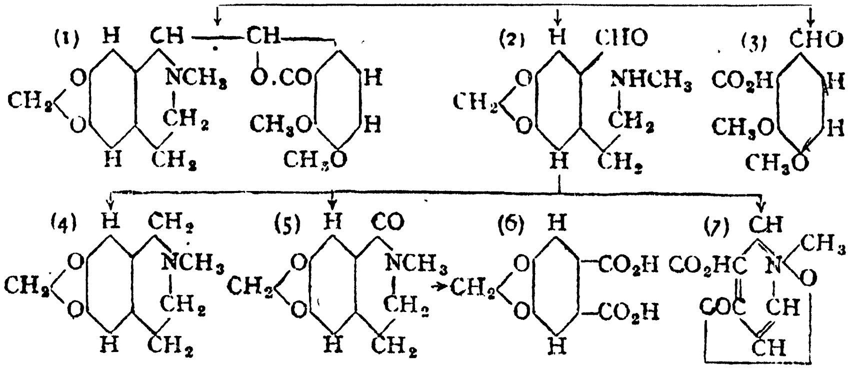
Narceïne (2), $C_{23}H_{27}NO_8 + 3H_2O$, m.p. 170° (anhydrous), is found, besides narcotine, in opium, and is obtained from narcotine iodomethylate (1), on treatment with KHO (A. **286,** 248; C. 1899, II. 390):



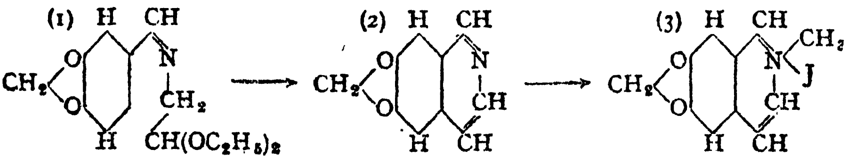
Compare the analogous transformation of cinchonine methiodide into methylcinchotoxine.

Hydrastine (1), $C_{21}H_{21}NO_6$ (see scheme below), m.p. 132°, $[\alpha]_D = -67°$ in chloroform (Durand, 1851), is found, besides berberine, in *Berberis vulgaris* and in the root of *Hydrastis canadensis*, a North American plant belonging to the *Ranunculaceæ* (C. 1899, II. 122). Hydrastine has a constitution resembling that of narcotine, from which it only differs by containing one methoxyl group less. On oxidation it splits up into opianic acid (3) and **hydrastinine** (2), m.p. 116°, which is the physiologically active part of hydrastine. Hydrastinine reacts like cotarnine, partly as a cyclic alkamine, partly as an amino-aldehyde. The formation of salts occurs with elimination of water, and produces real dihydro-*iso*-quinolinium salts.

On reduction, hydrastinine passes into hydrohydrastinine (4) or N-*methyl*-Bz-2,3-*methylenedioxytetrahydro*iso*quinoline*. On oxidation with potassium permanganate, hydrastinine first produces oxy-hydrastinine (5) and then hydrastinic acid, which, with nitric acid, is converted into the methylimide of hydrastic acid (6) or 4,5-*methylenedioxyphthalic acid*. On the synthesis of hydrastic acid, see C. 1907, II. 602; B. **43,** 1336. Hydrastinine itself is oxidized by nitric acid, like cotarnine, to apophyllenic acid (7) (W. Roser, A. **249,** 172; Freund, A. **271,** 311):

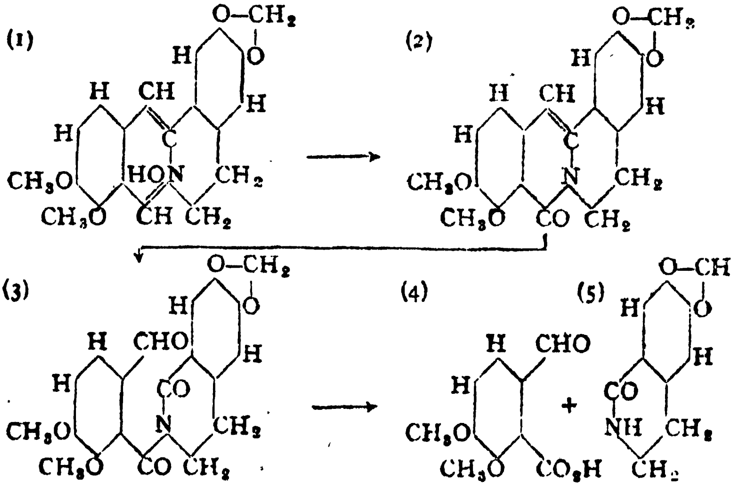


Synthesis of Hydrastinine.—Piperoxylideneaminoacetal (1) condenses with concentrated H_2SO_4 to Bz-2,3-*methylenedioxy*iso*quinoline* (2), which, on reduction of its iodo-methylate (3) with tin and HCl, passes into **hydro-hydrastinine,** m.p. 60°–61°. The latter is converted into hydrastinine with potassium bichromate and sulphuric acid (Fritsch, A. **286,** 18):

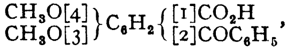


On recent syntheses of hydrastinine, see C. 1911, II. 171, 1816.

Berberine (1), $C_{20}H_{19}NO_5 + 5H_2O$, m.p. 145° with dec., is found in the roots of *Berberis vulgaris* and in many other plants. It is optically inactive. Of the numerous decomposition products due to oxidation with $KMnO_4$, we may mention *oxyberberine* (2) and *berberal* (3) as constitutionally important. The latter, boiled with dilute sulphuric acid, decomposes into *pseudo*-opianic acid (4), isomeric with opianic acid, and the lactam of ω-amino-ethyl-methylenedioxybenzoic (5), the constitution of which has been cleared up by conversion into oxyhydrastinine (W. H. Perkin, junior, J. Ch. Soc., **55**, 63; **57**, 991):



The positions of the two methoxyl groups follows from the formation of **2-Benzoyl-3,4-dimethoxy-benzoic acid,**



$\left.\begin{matrix}CH_3O[4]\\CH_3O[3]\end{matrix}\right\}C_6H_2\left\{\begin{matrix}[1]CO_2H\\[2]COC_6H_5\end{matrix}\right.$,

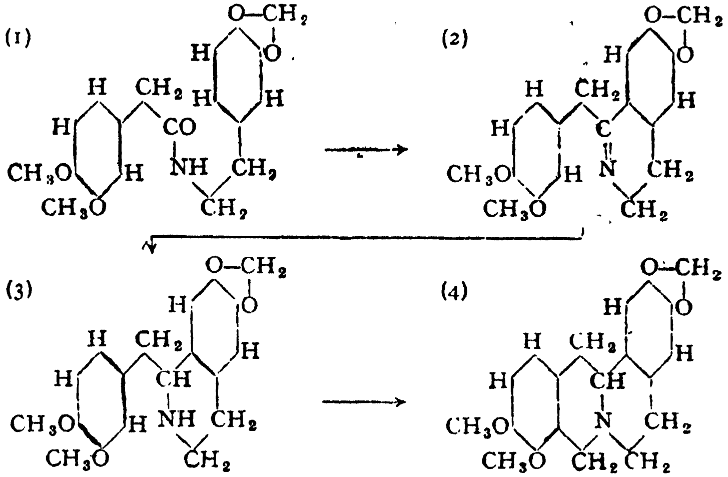
during the oxidation by $KMnO_4$ of phenyldihydroberberine, which is obtained by the action of C_6H_5MgBr upon berberine (C. 1910, II. 888).

The free berberinium base separated out from berberinium salts seems only to be stable in solution, and on evaporation passes into a "pseudo-ammonium" base, which, like cotarnine and hydrastinine, is to be regarded either as a cyclic alkamine or as an amino-aldehyde, sometimes called *berberinal* (C. 1911, II. 879):

$$—CH{=}\overset{|}{N}(OH)—CH_2— \longrightarrow —CH(OH)—\overset{|}{N}—CH_2— \text{ or } —CHO\ H\overset{|}{N}—CH_2.$$

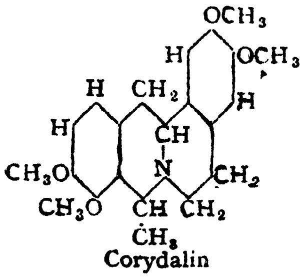
As an amino-aldehyde, berberine forms with hydroxylamine and *p*-amino-dimethyl-aniline an oxime and a dimethyl-amino-anil (C. 1905, I. 939), and condenses with ketones with evolution of water (compare acetoneberberine, C. 1911, II. 1865). On heating with alkali, berberine yields dihydroberberine and oxyberberine. Berberine has dyeing properties. It forms brownish-yellow needles. On reduction it yields the colourless *tetrahydroberberine*, $C_{20}H_{21}NO_4$, the racemic form of *Canadine*, contained in the root of *Hydrastis canadensis*, besides hydrastine. By means of its bromo-campho-sulphonate, tetrahydroberberine has been split up into *d*- and *l*-canadine (C. 1910, I. 1261). On heating berberine hydrochloride to 200° in a stream of CO_2, methyl chloride is split off, and a dark red phenol betaïne, the so-called *berberubin*, $C_{19}H_{13}NO_4$, is formed, from which methyl iodide regenerates berberine hydriodide (C. 1910, II. 166). On the action of magnesium-organic compounds upon berberine, see B. **38,** 2652; **40,** 2604.

Synthesis of Berberine (A. Pictet, B. **44,** 2480).—Homo-piperonylamine, $(CH_2O_2):C_6H_3.CH_2.CH_2NH_2$, condenses with homo-veratric acid chloride, $(CH_3O)_2C_6H_3CH_2.CH_2COCl$, in the presence of alkali to form homo-veratroyl-homo-piperonylamine (1), which, on boiling with P_2O_5 in xylene, passes into the dihydro*iso*quinoline base (2). Reduction with tin and HCl converts the latter into the tetrahydro-*iso*-quinoline base (veratryl-norhydrastinine) (3), which condenses with methylal and HCl to tetrahydroberberine (4), which, on gentle oxidation, yields berberin:



Synthesis of oxyberberine, see B. **44,** 2036.

From the roots of *Corydalis cava* numerous alkaloids have been isolated which are closely related, partly to berberine, partly to apomorphine. Only the most important of these are mentioned here. Their constitution has been mainly determined by J. Gadamer.



Corydalin

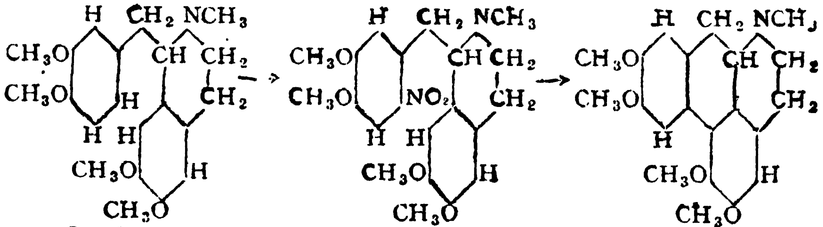
Corydaline, $C_{18}H_{15}N(OCH_3)_4$, m.p. 134°, $[\alpha]_D = +300°$, colourless prisms. On slight oxidation it passes into the yellow **dehydro-corydaline,** $C_{22}H_{25}O_5N$, corresponding to berberine. Stronger oxidation with

$KMnO_4$ produces **corydaldine,** ω-*aminoethylveratric acid lactam,*
$$\left.\begin{matrix} CH_3O[3] \\ CH_3O[4] \end{matrix}\right\} C_6H_2 \left\{\begin{matrix} [1]CO.NH \\ [6]CH_2.CH_2 \end{matrix}\right.$$ (C. 1905, II. 54).

Corybulbine, $C_{18}H_{15}N(OH)(OCH_3)_3$, m.p. 237°, contains a free phenol-hydroxyl, and passes on methylation into corydaline (C. 1901, I. 185).

The following corydalis alkaloids are closely related to apomorphine: **Corytuberine,** $C_{17}H_{13}N(OH)_2(OCH_3)_2$; **Glaucine,** $C_{17}H_{13}N(OCH_3)_4$; **Corydine,** $C_{17}H_{13}N(OH)(OCH_3)_3$; **Bulbocapnine,** $C_{17}H_{13}N(OH)(OCH_3)(O_2CH_2)$. Exhaustive methylation and subsequent oxidation disintegrates these alkaloids, like apomorphine, into phenanthrene carboxylic acids (C. 1912, I. **35,** 147, 149).

Special interest attaches to the conversion of laudanosine into glaucine in view of the possibility of the formation of the phenanthrene ring in plants. The nitro-laudanosine obtained by the nitration of laudanosine yields on reduction, diazotation, and boiling with powdered copper, racemic glaucine (see phenanthrene synthesis). By means of tartaric acid this is split up into *d*- and *l*-glaucine, the *d*-modification being identical with natural glaucine (C. 1912, I. 150):



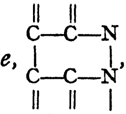
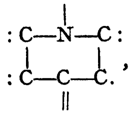
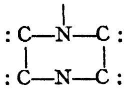
Laudanosin Glaucin

B. POLYHETERO-ATOMIC SIX-MEMBERED RINGS.

Polyhetero-atomic six-membered rings, containing oxygen and sulphur as ring members, occur in a series of bodies which have already been discussed at the conclusion of allied bodies. Dialkylene ethers—*e.g.*, *diethylene oxide*—and the anhydrides of α-oxyacids—*e.g.*, *glycollide, diglycollic anhydride*—contain rings consisting of four carbon atoms and two oxygen atoms. The six-membered ring of *diethylene disulphide* and of thianthrene or diphenylene disulphide contains two sulphur atoms, while three oxygen atoms or three sulphur atoms are present in the polymeric aldehydes and the thioaldehydes—*e.g.*, *trioxymethylene, trithiomethylene, paraldehyde, trithioaldehyde.*

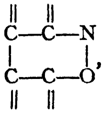
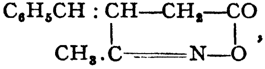
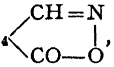
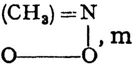
AZINES.

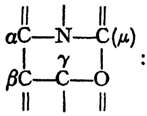
Those members of this division containing N-atoms as ring members require more exhaustive consideration. This was done also with like bodies of the five-membered series. They may be regarded, like the azoles, as derived from furan, thiophen, and pyrrole by the replacement of methin groups of monohetero-atomic rings, and accordingly they can be grouped under the common name of *azines.*

The *oxazines, oxdiazines* (azoxazines), and *dioxdiazines* are, then, the rings with the hetero-atoms: N and O, 2N and O, 2N and 2O; the *thiazines* and *thiodiazines* are the rings with the hetero-atoms S and N, S and 2N; and the *diazines*, *triazines*, and *tetrazines* are the six-membered rings with 2, 3, and 4 N-atoms. The position isomerides of dihetero-atomic azines are distinguished according to the position of the hetero-atoms with reference to one another by the prefixes ortho-, meta-, and para-. Thus, the three possible diazins as *ortho-diazine*, , *metadiazine*, , and *paradiazine*,  (B. **22**, 2083; A. **249**, 1; J. pr. Ch. **38**, 185); the oxazines as *orthoxazines*, *metoxazines*, *paroxazines;* the thiazines as *orthothiazines*, *metathiazines*, and *parathiazines*.

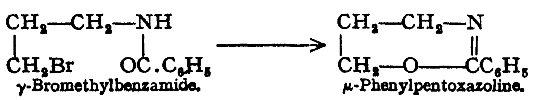
The parent substances of important classes of dyes (compare *resorufin*, *methylene blue*, *toluylene red*, *safranines*, *indulines*) are the dibenzo-derivatives of the paroxazines, parathiazines, and paradiazines.

1. OXAZINES.

A. The ring of **orthoxazine,** , is present in the oxime anhydrides of the γ-aldehydo- and γ-ketonic acids—*e.g.*, benzallævuloxime, , which bear the same relation to the oxime anhydrides of the β-ketonic acids, the isoxazolones, as the δ-lactones to the γ-lactones (B. **25**, 1930). The ring formation of the oximes of *o*-benzaldehydo- and *o*-benzo-keto-carboxylic acids occurs without difficulty. Derivatives of *benzorthoxazines* are produced: **Benzorthoxazinone,** o-*Benzaldoxime carboxylic anhydride*, , is derived from phthalaldehydic acid. It readily rearranges itself to the isomeric phthalimide (B. **24**, 2347). There is an intermediate formation of *o*-cyanobenzoic acid (see the indoxazenes). **Benzomethylorthoxazinone,** o-*Acetophenonoxime carboxylic anhydride*, , melts at 179 (B. **16**, 1995).

B. The following contain the **Metoxazine** ring,  :

I. The *pentoxazolines*, which are produced by the splitting-off of HBr from the γ-bromalkylamides. This is similar to the formation of the five-membered oxazolines from the β-bromalkylamides (B. **24**, 3213):

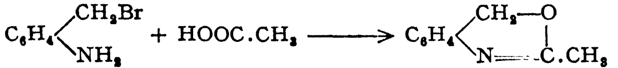


γ-Bromethylbenzamide. μ-Phenylpentoxazoline.

μ-Phenyl-α-methylpentoxazoline, $C_4H_5NO(CH_3)(C_6H_5)$, and **μ-Phenyl-α-dimethyl-γ-methylpentoxazoline,** $C_4H_3NO(CH_3)_3(C_6H_5)$, melting at 32°, are obtained from γ-chlorobutyl- and γ-brom*iso*hexylbenzamide.

μ-Allylamino- and **μ-phenylamino-γ-methylpentoxazoline,** or N-*allyl* and N-*phenyl butylene-ψ-urea*, $\begin{array}{l}CH_2\text{———}CH_2\text{—}N\\ |\qquad\qquad\qquad\quad \|\\ CH(CH_3)\text{—}O\text{——}C(NHR)\end{array}$, are obtained from γ-chlorobutylamine by means of allyl- and phenyl-mustard oil (B. **29,** 1428; **30,** 1319).

II. Derivatives of *benzometoxazine* or *phenopentoxazoline* are formed from *o*-amino-benzylhalogenides and acid anhydrides (B. **27,** 3515):

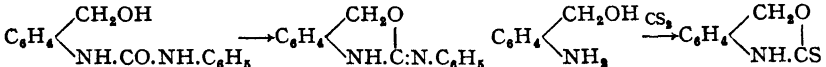

$$C_6H_4<\begin{array}{l}CH_2Br\\ NH_2\end{array} + HOOC.CH_3 \longrightarrow C_6H_4<\begin{array}{l}CH_2\text{—}O\\ N\text{=\!=}C.CH_3\end{array}$$

o-Aminobenzyl Bromide. μ-Methylphenopentoxazoline.

The *cumazonic acids* (B. **16,** 2585) also belong here—*e.g.*, **μ-Methyl cumazonic acid,** *Benzotrimethylmetoxazine,* $C_6H_4<\begin{array}{l}C(CH_3)_2\text{—}O\\ N\text{=\!=\!=}C.CH_3\end{array}$, melting at 218°, and **μ-Phenyl cumazonic Acid,** *Benzodimethyl-μ-phenyl-metoxazine,* $C_6H_4<\begin{array}{l}C(CH_3)_2\text{—}O\\ N\text{=\!=\!=}C.C_6H_5\end{array}$, melting at 220°, which have been obtained from 3-amino-4-oxypropyl-benzoic acid with acetyl chloride and benzoyl chloride. Carbon dioxide is liberated.

The acylanthranils must be regarded as αβ-**benzometoxazones. μ-Phenyl-βγ-benzo-metoxazone,** $C_6H_4<\begin{array}{l}CO.N\\ O\text{—}C.C_6H_5\end{array}$, m.p. 106°, is formed by the action of gaseous HCl upon O- and N-benzoyl salicylic acid amide (C. 1910, I. 1263).

The *imino-* and *thio-cumazones* are derivatives of *dihydrobenzometoxazine.* The former result upon the exit of water from the urea derivatives of *o*-aminobenzyl alcohol, the latter by the action of CS_2 upon the alcoholic solution of *o*-aminobenzyl alcohol and related compounds:


$$C_6H_4<\begin{array}{l}CH_2OH\\ NH.CO.NH.C_6H_5\end{array} \longrightarrow C_6H_4<\begin{array}{l}CH_2O\\ NH.C{:}N.C_6H_5\end{array} \qquad C_6H_4<\begin{array}{l}CH_2OH\\ NH_2\end{array} \xrightarrow{CS_2} C_6H_4<\begin{array}{l}CH_2O\\ NH.CS\end{array}$$

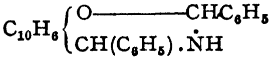
Phenyl-imino-cumazone. Thiocumazone.

The imino-cumazones are isomeric with the keto-tetrahydroquinazolines, and when digested with aromatic amines become quinazoline compounds. The O-member is replaced by NR. The thiocumazones behave similarly (B. **27,** 2424).

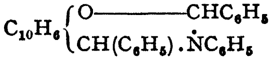
Phenyl-imino-cumazone, *Benzodihydrometoxazine anil,* $C_8H_7ON{:}(NC_6H_5)$, melting at 146° (B. **22,** 2938), forms stable salts with acids; with acid anhydrides and chlorides it yields addition products. **Thiocumazone, Benzo-dihydro-thiometoxazine,** $C_8H_7ON:S$, melting at 142°, is an acid, and forms a sparingly soluble potassium salt (B. **25,** 2979; **27,** 1866).

μ-Methyl- and **μ-phenyl-βγ-benzo-dihydro-metoxazone,** $C_6H_4<\begin{array}{l}O\text{——}CH.R\\ CO\text{—}NH\end{array}$, m.p. 146° and 169°, are formed by the condensation of acetaldehyde and benzaldehyde with salicylic acid amide (C. 1907, II. 1341).

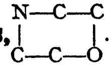
Naphtho-βγ-dihydro-metoxazines are formed by the condensation of β-naphthols with aldehydes, NH_3, or amines (C. 1901, II. 1009):

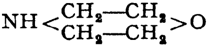


$$C_{10}H_6\begin{cases}O\text{———}CHC_6H_5\\CH(C_6H_5).\dot{N}H\end{cases}$$

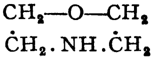


$$C_{10}H_6\begin{cases}O\text{———}CHC_6H_5\\CH(C_6H_5).\dot{N}C_6H_5\end{cases}$$

C. **Paroxazines,**  $\begin{matrix}N\text{—}C\text{—}C\\|\quad\quad\ \ |\\C\text{—}C\text{—}O\end{matrix}$.

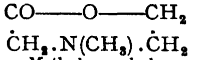
I. Of the simple nucleus, we know only saturated derivatives. *Tetrahydro-paroxazine* or **morpholine,**  $NH<\begin{matrix}CH_2\text{—}CH_2\\CH_2\text{—}CH_2\end{matrix}>O$, b.p. 129°, was so called because, for some time, a similar ring was supposed to exist in morphine. It is formed from diethylolamine, $NH(CH_2CH_2OH)_2$ (see Vol. I.), by heating with 70 per cent. sulphuric acid to 160° to 170°. It is better to start from toluenesulphondinaphthoxyethylamide $(C_{10}H_7OCH_2CH_2)_2NSO_2C_7H_7$, which is formed from bromethyl-β-naphthol ether, $C_{10}H_7OCH_2CH_2Br$, with toluenesulphonamide, and gives morpholine on heating with mineral acids (B. **34,** 1157). Morpholine closely resembles piperidine. By exhaustive methylation it is split up into trimethylamine, acetylene, and water (A. **301,** 1; B. **32,** 736).

Keto-derivatives of morpholine are represented by *N*-**methylmorpholone,** b.p. 233°, from oxethylmethylamino-acetic acid (A. **307,** 199); **diglycollic acid imide**; and the isomeric **diglycollimide acid anhydride** (see Vol. I.):



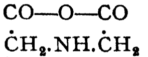
$$\begin{matrix}CH_2\text{—}O\text{—}CH_2\\\dot{C}H_2.NH.\dot{C}H_2\end{matrix}$$

Morpholine.



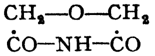
$$\begin{matrix}CO\text{——}O\text{——}CH_2\\\dot{C}H_2.N(CH_3).\dot{C}H_2\end{matrix}$$

Methyl-morpholone.



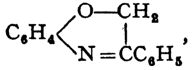
$$\begin{matrix}CO\text{—}O\text{—}CO\\\dot{C}H_2.NH.\dot{C}H_2\end{matrix}$$

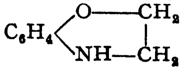
Diglycolamic acid anhydride.

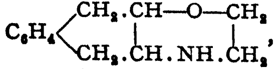


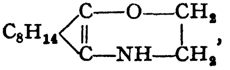
$$\begin{matrix}CH_2\text{—}O\text{—}CH_2\\\dot{C}O\text{—}NH\text{—}\dot{C}O\end{matrix}$$

Diglycollic acid imide.

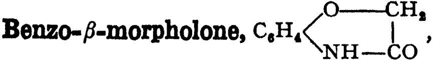
II. *Benzoparoxazine* has the derivatives: **β-phenylbenzoparoxazine,**  $C_6H_4<\begin{matrix}O\text{—}CH_2\\|\\N{=}CC_6H_5\end{matrix}$, m.p. 103°, obtained by the reduction of *o*-nitrophenyl phenacyl ether, $(NO_2)C_6H_4OCH_2COC_6H_5$; and **β-methylbenzoparoxazine,** C_9H_9NO, similarly obtained from *o*-nitrophenoxyacetone. Stronger reduction in the latter case produces β-methylbenzomorpholine, $C_9H_{11}NO$, b.p. 255° (B. **31,** 752).

Benzomorpholine,  $C_6H_4<\begin{matrix}O\text{——}CH_2\\|\\NH\text{—}CH_2\end{matrix}$, b.p. 268°, from o-*hydroxyethylaminophenol;* on decomposition by iodo-methylate, it gives o-*dimethylaminophenyl vinyl ether,* $(CH_3)_2NC_6H_4O.CH:CH_2$; benzomorpholine resembles tetrahydroquinoline (B. **32,** 732).

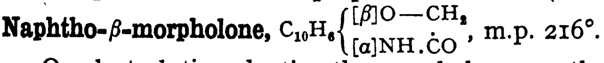
The combination of tetrahydro-naphthylene oxide with amino-ethyl alcohol produces the so-called **naphthalane-morpholine,**  $C_6H_4<\begin{matrix}CH_2.CH\text{—}O\text{—}CH_2\\|\quad\quad\quad\quad|\\CH_2.CH.NH.CH_2\end{matrix}$, m.p. 63°, b.p. 312°, which, like morphine, is soporific. Decomposition by exhaustive methylation converts it into *dihydronaphthyl dimethylaminoethyl ether,* $C_{10}H_9O.CH_2CH_2.N(CH_3)_2$, which resembles methylmorphimethine in its decomposition into naphthaline and dimethylamino ethyl alcohol, which, however, in this case occurs much more easily (B. **32**, 742; A. **307**, 171). Amino-camphor and ethylene oxide produce camphene-morpholine,



$C_8H_{14}\left\langle\begin{matrix}C-O-CH_2\\ \| \qquad\quad | \\ C-NH-CH_2\end{matrix}\right.$, b.p. 242° (A. **307**, 187).



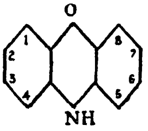
Benzo-β-morpholone, $C_6H_4\left\langle\begin{matrix}O-CH_2\\ \qquad | \\ NH-CO\end{matrix}\right.$, from o-nitrophenoxyacetic acid (see C. 1898, II. 540). The two isomers, **Benzo-α-methyl-β-morpholone** and **benzo-β-methyl-α-morpholone,** m.p. 145° and 110° respectively, are obtained from o-nitrophenoxypropionic acid and from o-aminophenol with bromopropionic acid ester (B. **30**, 2927; **33**, 1598).



Naphtho-β-morpholone, $C_{10}H_6\begin{cases}[\beta]O-CH_2\\ [\alpha]NH.\dot{C}O\end{cases}$, m.p. 216°.

On electrolytic reduction the morpholones partly yield morpholines and partly split the hetero-ring (C. 1903, II. 447).

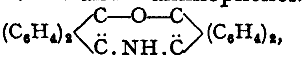
III. A series of important dyestuffs belong to the group of dibenzo-paroxazine or phenoxazine, of benzo-naphtho- and dinaphtho-paroxazine.



Phenoxazin.

Phenoxazine, m.p. 148°, is formed by heating o-aminophenol with catechol (A. **322**, 9).

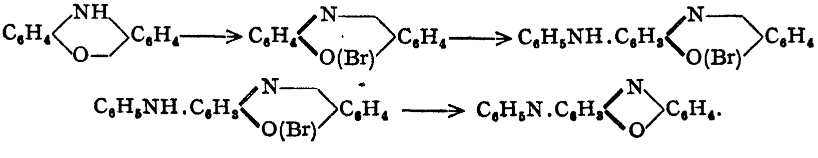
3-**Methylphenoxazine,** m.p. 124°, from catechol and o-amino-m-cresol; 3,6-**dimethylphenoxazine,** m.p. 205°, from homocatechol and o-amino-m-cresol. 4-**Nitrophenoxazine,** m.p. 166°, from o,p-dinitro-o_1-hydroxydiphenylamine, on heating with dilute NaHO with elimination of NO_2H (A. **366**, 80). Similarly, 2,4-**dinitrophenoxazine** is obtained from picryl chloride and o-aminophenol.



Phenanthroxazine, $(C_6H_4)_2\left\langle\begin{matrix}C-O-C\\ \ddot{C}.NH.\ddot{C}\end{matrix}\right\rangle(C_6H_4)_2$, from phenanthrene hydro-quinone with NH_3 (B. **34**, 535).

Phenoxazine and its homologues are oxidized by bromine or ferric chloride to coloured ortho-quinoid so-called azoxonium salts (with quadrivalent oxygen), which mostly are very unstable. Especially when the para-positions to the N-atom are free from substitution, substitution easily takes place in these positions on treatment with amines or alkalies by the groups —NHR and —OH.

Thus the *Dyes of the Paroxazine Series* are produced, which form inner anhydrides by splitting off 1 molecule of acid (A. **322**, 1)—*e.g.:*



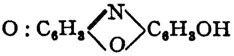
$$C_6H_4\left\langle\begin{matrix}NH\\ O\end{matrix}\right\rangle C_6H_4 \longrightarrow C_6H_4\left\langle\begin{matrix}N\\ O(Br)\end{matrix}\right\rangle C_6H_4 \longrightarrow C_6H_5NH.C_6H_3\left\langle\begin{matrix}N\\ O(Br)\end{matrix}\right\rangle C_6H_4$$

$$C_6H_5NH.C_6H_3\left\langle\begin{matrix}N\\ O(Br)\end{matrix}\right\rangle C_6H_4 \longrightarrow C_6H_5N.C_6H_3\left\langle\begin{matrix}N\\ O\end{matrix}\right\rangle C_6H_4.$$

This interpretation of the paroxazine dyes as *ortho-quinones*, which may be equally applied to the parathiazine and paradiazine dyes (see below), is in contrast with the older theory, which regards these compounds as paraquinones and derivatives of the quinone anils, indophenols, and indamines, in which the two aromatic nuclei, in the ortho-position with respect to the tertiary N-atom, are linked by an oxygen atom—*e.g.*:

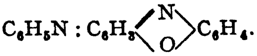
$O : C_6H_4{=}N{-}C_6H_4OH$

Indo-phenol.



$O : C_6H_3\left\langle\begin{smallmatrix}N\\O\end{smallmatrix}\right\rangle C_6H_3OH$

Oxy-phenoxazone (Resorufin).

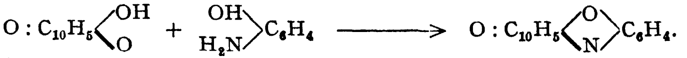


$C_6H_5N : C_6H_3\left\langle\begin{smallmatrix}N\\O\end{smallmatrix}\right\rangle C_6H_4.$

Phenyl-phenoxazime.

Perhaps the ortho-quinoid anhydride forms are desmotropic with the para-quinoid forms; the latter, for the sake of convenience, have been retained in what follows. For the phenoxazime salts the para-quinoid constitution may be preferable. Accordingly, as quinone monimine or quinone di-imine derivatives are in question, the ground substances of the phenoxazine dyes are distinguished as phenoxazones or phenoxazimes (B. **25,** 2995). They are also produced:

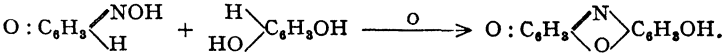
1. Upon condensing *o*-hydroxyquinones and *o*-hydroxyquinone-imines with *o*-aminophenols. The hydroxy-*p*-quinones of the naphthalene series are especially adapted for these condensations (B. **26,** 2375; **28,** 353):



$$O : C_{10}H_5\left\langle\begin{smallmatrix}OH\\O\end{smallmatrix}\right. + \left.\begin{smallmatrix}OH\\H_2N\end{smallmatrix}\right\rangle C_6H_4 \longrightarrow O : C_{10}H_5\left\langle\begin{smallmatrix}O\\N\end{smallmatrix}\right\rangle C_6H_4.$$

α,*o*-Hydroxynaphthoquinone. *o*-Aminophenol. Naphthophenoxazone.

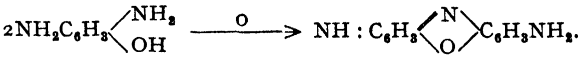
2. Oxy- and amino-derivatives of the phenoxazones and phenoxazimes, the real dyes, result by the condensation of quinone dichlorimides, nitrosophenols, or nitrosodimethyl aniline with polyhydric phenols or tertiary aminophenols:



$$O : C_6H_3\left\langle\begin{smallmatrix}NOH\\H\end{smallmatrix}\right. + \left.\begin{smallmatrix}H\\HO\end{smallmatrix}\right\rangle C_6H_3OH \xrightarrow{O} O : C_6H_3\left\langle\begin{smallmatrix}N\\O\end{smallmatrix}\right\rangle C_6H_3OH.$$

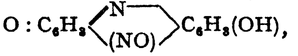
Nitrosophenol. Resorcin. Hydroxyphenoxazone.

3. Aminophenoxazimes are obtained by air oxidation of hydroxy-*p* phenylene diamines in acetic acid solution (B. **40,** 3397; **42,** 1275):



$$2NH_2C_6H_3\left\langle\begin{smallmatrix}NH_2\\OH\end{smallmatrix}\right. \xrightarrow{O} NH : C_6H_3\left\langle\begin{smallmatrix}N\\O\end{smallmatrix}\right\rangle C_6H_3NH_2.$$

Phenoxazone, $O[3]C_6H_2(NO)C_6H_4$, m.p. 217°, golden-brown flakes; phenoxazine with $FeCl_3$ gives the unstable phenoxazonium chloride (see above), which, on boiling with water, yields phenoxazone (B. **35,** 341).

Resorufin, Hydroxyphenoxazone, $O : C_6H_3(NO)C_6H_3(OH)$, is produced when nitric acid containing N_2O_3 acts upon an ethereal solution of resorcin (Weselsky, A. **162,** 273); and from nitrosoresorcin by means of resorcin (B. **24,** 3366). *Resazurin,*  $O : C_6H_3\left\langle\begin{smallmatrix}N\\(NO)\end{smallmatrix}\right\rangle C_6H_3(OH)$, is an intermediate product in this reaction. The alkaline solutions of resorufin are rose-red, with a magnificent cinnabar-red fluorescence. **Orcirufin** is obtained, like resorufin, from orcin.

Phenylphenoxazime, $C_6H_5N[3]C_6H_3(NO)C_6H_4$, red flakes, m.p. 197°, from phenoxazine by oxidation with $FeCl_3$ in the presence of an aniline salt, is converted by further action of aniline into **anilinophenylphenoxazime,** $C_6H_5N[3]C_6H_3(NO)C_6H_3[6]NHC_6H_5$, which resembles the dyes of the Capri Blue series, which are also derived from 3,6-diaminophenoxazine—*e.g.*, $(CH_3)_2NC_6H_3(NO)C_6H_2(CH_3)N(C_2H_5)_2$, whose zinc chloride double salt, obtained from *o*-diethylamino-*m*-cresol and nitrosodimethylaniline, is the *Capri Blue* G.O.N. of commerce (C. 1902, II. 458).

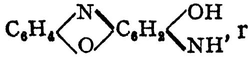
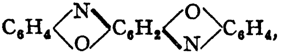
Gallocyanine, *Dimethylamino-hydroxy-phenoxazone-carboxylic acid*, $N(CH_3)_2.C_6H_3(NO)C_6H(OH)COOH:O$, is produced by the action of nitrosodimethylaniline upon gallic acid. With mordants, especially chromic oxide, it forms violet-coloured and stable *lakes* (calico printing).

On heating with aqueous sodium acetate, soda, etc., gallocyanine expels CO_2 and passes into dimethylaminohydroxyphenoxazone (C. 1908, I. 573). On the products of the action of primary aromatic amines upon the gallocyanine dyes, see J. pr. Ch. [2], **77,** 498.

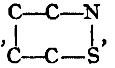
Phenonaphthoxazone, $O:C_{10}H_5(NO)C_6H_4$, m.p. 192°. **Naphthophenoxazone,** $O:C_6H_3(NO)C_{10}H_6$, brown needles, m.p. 211°, from nitrosophenol and *β*-naphthol (B. **36,** 1807). **Phenonaphthoxazime,** $NHC_{10}H_5(NO)C_6H_4$, m.p. 243°, from hydroxynaphthaquinone-imine with *o*-aminophenol.

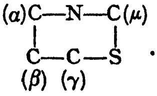
Chlorohydroxyphenoxazone, $C_6H_4(NO)C_6HCl(OH):O$, melting with decomposition at 235°, is obtained from *p*-dihydroxychloroquinone and aminophenol (B. **26,** 2375).

Dimethylnaphthophenoxazime chloride, $C_{10}H_6(NO)C_6H_3:N(CH_3)_2Cl$, from *β*-naphthol and nitrosodimethylaniline, is the so-called *naphthol blue*, which dyes cotton mordanted with tannin a violet-blue (B. **23,** 2247). *Nile blue* is an amino-derivative of naphthol blue, while *cyanamine* is an anilino-derivative. For other derivatives consult A. **289,** 90; B. **29,** R. 1,000).

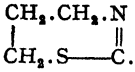
Hydroxyphenoxazime,  $C_6H_4{<}\begin{smallmatrix}N\\O\end{smallmatrix}{>}C_6H_2{<}\begin{smallmatrix}OH\\NH\end{smallmatrix}$, results from the oxidation of *o*-aminophenol. It condenses to **triphenodioxazine,**  $C_6H_4{<}\begin{smallmatrix}N\\O\end{smallmatrix}{>}C_6H_2{<}\begin{smallmatrix}O\\N\end{smallmatrix}{>}C_6H_4$, with another molecule of aminophenol; B. **23,** 182, **27,** 2784; **32,** 126). See B. **29,** 2076, for **methyltriphenodioxazine.**

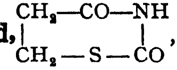
2. THIAZINES.

A. **Orthothiazines,**  $\begin{matrix}C-C-N\\ | \qquad | \\ C-C-S\end{matrix}$, are not known.

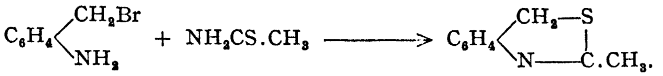
B. **Metathiazine,**  $\begin{matrix}(\alpha)C-N-C(\mu)\\ | \qquad | \\ C-C-S\\ (\beta)\ (\gamma)\end{matrix}$. The following bodies are derived from this ring:

I. The *penthiazolines*, corresponding to the pentoxazolines. They are prepared from the *γ*-haloid alkylthiobenzamides.

μ-Phenylpenthiazoline, , melting at 45°, is obtained from thiobenzamide and trimethylene chlorbromide (B. **26,** 1077). **μ-Phenyl-α-dimethyl-γ-methylpenthiazoline,** $C_4H_3NS(CH_3)_3(C_6H_5)$, melting at 34°, is derived from γ-brom*iso*hexylthiobenzamide. **μ-Mercapto-γ-methylpenthiazoline** and **-γ-methyl-α-dimethylpenthiazoline,** melting at 131° and at 180°, are made from γ-chlorbutylamine and γ-brom*iso*hexylamine by the action of carbon bisulphide (B. **29,** 1429; **30,** 1321; see also B. **29,** R. 648 and 684).

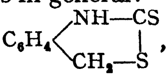
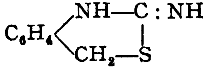
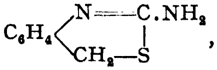
Diketo-penthiazolidine, Sinapane-propionic Acid, , melting at 159°, results when β-iodopropionic acid acts upon xanthogenamide (B. **24,** 3848).

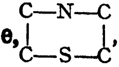
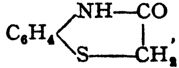
II. Derivatives of *benzometathiazine* or *phenpenthiazole* are produced in the interaction of *o*-aminobenzyl haloids and thio-amides (I. 282; II. 251) (B. **27,** 3519):



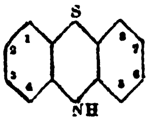
μ-Methylphenpenthiazole, melting at 46°, is produced by the action of P_2S_5 upon μ-methylphenopentoxazole; also from *o*-acetylaminobenzyl alcohol and P_2S_5, as well as from *o*-acetylaminobenzyl sulphide and PCl_5. Consult B. **30,** 1143, for other derivatives.

The *imino-* and *thio-cumothiazones,* corresponding to the imino- and thiocumazones, belong here. Like them, they result from the action of CS_2 and alcoholic potash upon the thio-urea derivatives of *o*-aminobenzyl alcohol, or aminobenzyl alcohols in general:

Thiocumothiazone, *Benzodihydrothiothiazine,* , melting at 166°, is an acid. It forms *N*-phenylthiotetrahydroquinazoline when boiled with aniline, the ring sulphur atom being replaced by NC_6H_5. **Iminocumothiazone,** *Benzylene-ψ-thiourea,*  or , melting at 137°, is produced in the reduction of *o*-nitrobenzyl sulphocyanide, as well as from *o*-aminobenzyl chloride and thiourea. Potassium permanganate oxidizes it to α-quinazolone, while, digested with aniline, it forms **phenylimino-cumothiazone,** *benzodihydrothiazine anil,* melting at 197°, which results upon expelling water from ω-hydroxy-*o*-tolylphenylthiourea (B. **22,** 2933; **27,** 2429).

C. **Parathiazine,** , **Ketodihydrobenzothiazine,** , is a benzo-derivative which may possibly originate from this ring. It melts at 179°, and is produced by the interaction of *o*-aminothiophenol and bromacetic acid (B. **30,** 607).

The symmetrical dibenzo-derivatives—*e.g., dibenzo-* and *dinaphthoparathiazine,* or *thiodiphenylamine* and *thiodinaphthylamine*—are more important. Thiodiphenylamine corresponds to phenoxazine or dibenzoparoxazine, and, like the latter, is the parent substance of a series of more important dyes, among which is the very valuable methylene blue.



Thiodiphenylamine.

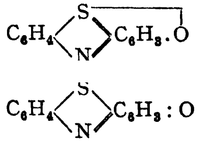
Thiodiphenylamine, melting at 150° and boiling at 370°, is prepared analogously to phenoxazine by heating *o*-aminothiophenol and pyrocatechol to 220°. An easier course consists in heating diphenylamine to 250° with sulphur in the presence of $AlCl_3$ (C. 1910, II. 255) or S_2Cl_2 (B. **21,** 2063). It is a neutral body, the imine hydrogen of which can be replaced by alkyl and acid radicals. See B. **24,** 2910, for the *urea derivatives.* **Tetrachlorothiodiphenylamine,** m.p. 235° (B. **29,** 1363). H_2O_2 oxidizes thiodiphenylamine to **diphenylamine sulphoxide,** $C_6H_4{<}\substack{SO\\NH}{>}C_6H_4$, m.p. 250°, which, with cold HCl, gives phenazothionium chloride (see below), and, with hot HCl, chlorothiodiphenylamine (C. 1909, II. 1326; 1910, II. 890). With nitric acid, thiodiphenylamine yields nitrodiphenylaminesulphoxide, $C_6H_4{<}\substack{SO\\NH}{>}C_6H_3.NO_2$, which can be reduced to 3-**amino-thio-diphenylamine,** and dinitro-diphenyl sulphoxide, which can be reduced to 3,6-**diaminothiodiphenylamine** or "*leucothionine,*" $NH_2.C_6H_3{<}\substack{S\\NH}{>}C_6H_3.NH_2$. The latter is also formed by heating *p*-diaminodiphenylamine, $(NH_2C_6H_4)_2NH$, with sulphur. It is the leuco-base of the simplest thionine dye, into which it is converted by oxidizing with $FeCl_3$. The tetra-methyl derivative of leucothionine is the leuco-base of methylene blue. The therapeutically active acidyl derivatives of leuco-methylene blue, like $N(CH_3)_2C_6H_4[N(COCH_3)S]C_6H_4N[CH_3]_2$, are easily obtained from the zinc chloride double salt of leuco-methylene blue with acid chlorides (B. **33,** 1567).

2,4-**Dinitrothiodiphenylamine,** from picryl chloride and *o*-aminothiophenol, gives, on reduction, an isomer of leucothionine (A. **322,** 57; B. **44,** 3011).

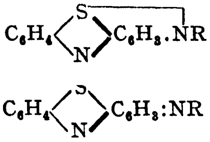
Thiophenyl-*α*- and *β*-naphthylamine, $C_6H_4(SNH)C_{10}H_6$, m.p. 138° and 178°, from phenyl-*α*- and *β*-naphthylamine with sulphur. **Thio-*α*- and *β*-dinaphthylamine,** $S(C_{10}H_6)_2NH$, m.p. 177° and 236°, from thio-*α*- and *β*-dinaphthylamine with sulphur (A. **322,** 44, 51).

By oxidation with $FeCl_3$ or bromine, thiophenylamine and its homologues, like phenoxazine, are converted into coloured ortho-quinoid so-called "*azothionium*" salts (with quadrivalent sulphur), $N{<}\substack{C_6H_4\\C_6H_4}{>}SCl, N{<}\substack{C_6H_4\\C_6H_4}{>}SBr$, which, like the azoxonium salts, are substituted, on treatment with amines or water, in the para-position, with respect to the N-atom, by NHR or OH groups.

As regards the structure of the *dyes of the thiazine series,* the same remarks apply as those concerning the paroxazine dyes: the dye bases can be regarded either as inner anhydrides of ortho-quinoid amino- or oxyphenazothionium hydroxides, or as derivatives of para-quinoid indophenols, indamines, etc. (compare A. **322,** 34):

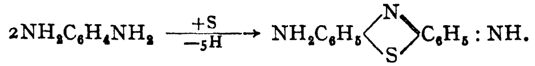


Phenothiazone.



Phenothiazime.

Lauth's dye substances belong to the phenothiazimes (Bernthsen, A. **230,** 73; **251,** 1). They result upon oxidizing *p*-phenylenediamines in the presence of hydrogen sulphide. It is probable that indamines occur as intermediate products:



Another procedure which may be adopted in the preparation of these dyestuffs is based upon the fact that indamines and thiosulphuric acid yield thiosulphonic acids, which change to the leuco-bases of the thiazine dyestuffs upon boiling them with dilute acids. Therefore, the dyestuffs can be obtained by oxidizing a mixture of 1 molecule of *p*-diamine with 1 molecule of a monamine, which form the indamine, in the presence of a thiosulphate. Pheno-thiazones are produced when *p*-aminophenols are oxidized in the presence of hydrogen sulphide.

Phenothiazime, $C_6H_4(NS)C_6H_3NH$, is obtained from 3-aminothiodiphenylamine by oxidation or by de-amination of thionine (see below). It reacts with amines in the cold, forming *N*-alkylated thionines, $NHRC_6H_3(NS)C_6H_3NH$ (C. 1900, II. 340; B. **33,** 3291). Pheno-thiazime chloride or 3-amino-phenazo-thionium chloride (see above) can be diazotised in a strongly acid solution (A. **322,** 64).

Phenylphenothiazime, $C_6H_4(NS)C_6H_3(NC_6H_5)$, dark red flakes, m.p. 150°, from thiodiphenylamine by oxidation with $FeCl_3$ in the presence of an aniline salt. Its chloride, 3-anilinophenazothionium chloride, yields, after further action of aniline, 3,6-*dianilinophenazothionium chloride* or diphenylthionine chloride (A. **322,** 39).

Aminophenothiazime, Thionine, *Lauth's Violet,* $NH_2.C_6H_3(NS)C_6H_3 : NH$, is obtained from *p*-phenylenediamine, and also from its leuco-base, diaminothiodiphenylamine, by oxidation.

Isomeric with thionine is **4-aminophenothiazime,** $C_6H_4(NS)C_6H_3(NH_2)NH$, obtained by oxidizing 2,4-diaminothiodiphenylamine (A. **322,** 57).

Methylene Blue, *Tetramethylaminophenothiazimium chloride,* $(CH_3)_2N.C_6H_3(NS)C_6H_3 : N(CH_3)_2Cl$ (Caro, 1877), results upon oxidizing 2 molecules of dimethyl-*p*-phenylenediamine in H_2S-solution, or 1 molecule of dimethyl-*p*-phenylenediamine with 1 molecule of dimethyl aniline and thiosulphate.

It dyes silk, or cotton mordanted with tannic acid, a beautiful *fast blue.*

Phenothiazone, $C_6H_4(SN)C_6H_3O$, results upon oxidizing hydroxythiodiphenylamine, or from phenothiazime by boiling in soda solution. **Pheno-α-naphthazothione,** $C_6H_4(NS)C_{10}H_5O$, m.p. 176°, from phenonaphthazothionium sulphate on standing in aqueous solution. **Dinaphthazo-thione,** $C_{10}H_6(NS)C_{10}H_5O$, m.p. 245°, from phenyldinaphthiazime by the action of dilute mineral acids (A. **322,** 52).

Oxyphenothiazone, Thionol, $HO.C_6H_3(NS)C_6H_3:O$, is produced on boiling thionin with dilute acids or alkalies.

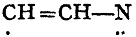
Also from hydroquinone, *p*-aminophenol, and sulphur, with subsequent oxidation. Hydroquinone, *p*-phenylene-diamine, and sulphur similarly give **thionoline,** $NH_2C_6H_3(NS)C_6H_3:O$ (C. 1899, II. 548).

The para-thiazine class probably comprises the blue and black substantive cotton dyes which are chiefly produced by fusing *p*-amino- and *p*-nitro-phenols, nitro- and nitroxy-diphenylamines, and indophenols, with sulphur and sulphur alkalies at temperatures between 140° and 200°. They are called Sulphur Dyes.* They are high molecular, amorphous dyes, insoluble in acids and alkalies. But when treated with sodium sulphide they dissolve even in the cold, and are precipitated unchanged from such solutions by blowing air through them. This behaviour renders it possible to use them in the manner of vat dyes. The resulting dull colorations are very fast with regard to light and washing, and this quality can be increased by treatment with chromium or copper salts. The constitution of the sulphur dyes is not yet determined with certainty. At present they are regarded as di- or poly-sulphide derivatives of thiazines, which, on treatment with sodium sulphide, form easily oxidizable mercaptothiazines soluble in alkali. That they belong to the thiazine group has been proved directly in the case of one of them, "Immedial Pure Blue" (see below), by converting it into tetrabromodimethylaminophenothiazone (B. **37,** 2617, 3032; see also B. **39,** 1016; D.R.P. 140964, 178940).

The first technically important sulphur dye, now obsolete, is "*Vidal Black,*" from *p*-aminophenol or *p*-amino-*o*-cresol (C. 1897, II. 747; 1898, II. 1151). Among the exceedingly numerous sulphur dyes we may mention Sulphur Black (from 2,4-dinitrophenol), Immedial Black (from *o*,*p*-dinitro-*p*-hydroxydiphenylamine), and Immedial Pure Blue (from *p*-hydroxy-*p*-dimethylaminodiphenylamine).

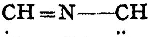
Another group of yellow and brown sulphur dyes, obtained chiefly by fusion of *m*-toluylene-diamine and related substances with sulphur or sulphur alkalies, probably belongs to the class of benzothiazoles.

3. DIAZINES.



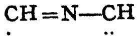
$$\begin{array}{l} CH{=}CH{-}N \\ \dot{C}H{=}CH{-}\ddot{N} \end{array}$$

Pyridazine,
Orthodiazine.



$$\begin{array}{l} CH{=}N{-}{-}CH \\ \dot{C}H{=}CH{-}\ddot{N} \end{array}$$

Pyrimidine,
Metadiazine.



$$\begin{array}{l} CH{=}N{-}CH \\ \dot{C}H{=}N{-}\ddot{C}H \end{array}$$

Pyrazine,
Paradiazine.

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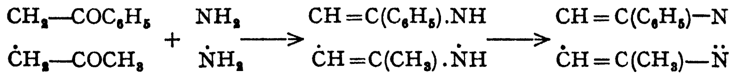
* O. Lange, "Die Schwefelfarbstoffe, ihre Herstellung und Verwendung," Leipzig, 1912.

A. ORTHODIAZINES.

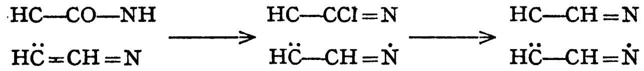
I. *Pyridazines* or ortho-diazines are formed:

1. From 1,4-diketones with hydrazine hydrate; the dihydropyridazines formed at first pass into pyridazines by air or auto-oxidation (B. **36**, 491):



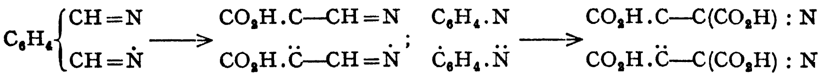
$$\begin{array}{l} CH_2—COC_6H_5 \\ \dot{C}H_2—COCH_3 \end{array} + \begin{array}{l} NH_2 \\ \dot{N}H_2 \end{array} \longrightarrow \begin{array}{l} CH=C(C_6H_5).NH \\ \dot{C}H=C(CH_3).\dot{N}H \end{array} \longrightarrow \begin{array}{l} CH=C(C_6H_5)—N \\ \dot{C}H=C(CH_3)—\ddot{N} \end{array}$$

2. From pyridazones (see below), with $POCl_3$, chloropyridazines are obtained, which are reduced to pyridazines with HI and phosphorus (B. **34**, 4227):

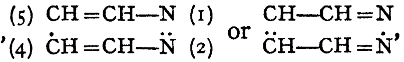


$$\begin{array}{l} HC—CO—NH \\ H\ddot{C}=CH=N \end{array} \longrightarrow \begin{array}{l} HC—CCl=N \\ H\ddot{C}—CH=\dot{N} \end{array} \longrightarrow \begin{array}{l} HC—CH=N \\ H\ddot{C}—CH=\dot{N} \end{array}$$

3. Phthalazines and phenazones, the benzo- and dibenzo-derivatives of pyridazine, are oxidized by means of permanganate to pyridazine carboxylic acids (B. **36**, 3373):



$$C_6H_4\left\{\begin{array}{l} CH=N \\ CH=\dot{N} \end{array}\right. \longrightarrow \begin{array}{l} CO_2H.C—CH=N \\ CO_2H.\ddot{C}—CH=\dot{N} \end{array} ; \quad \begin{array}{l} C_6H_4.N \\ \dot{C}_6H_4.\ddot{N} \end{array} \longrightarrow \begin{array}{l} CO_2H.C—C(CO_2H):N \\ CO_2H.\ddot{C}—C(CO_2H):N \end{array}$$



Pyridazine, o-*Diazine,* $\begin{array}{l} (5)\ CH=CH—N\ (1) \\ (4)\ \dot{C}H=CH—\ddot{N}\ (2) \end{array}$ or $\begin{array}{l} CH—CH=N \\ \ddot{C}H—CH=\dot{N} \end{array}$, m.p. −8°, b.p. 208°, is formed (1) from nitro-succinaldehyde or from the fumar-dialdehyde resulting from its decomposition, and hydrazine hydrate (C. 1903, I. 652); (2) from pyridazine-3-carboxylic acid; or (3) the tetra-carboxylic acid by splitting off the carboxyl groups; (4) from pyridazone by method 2 (B. **42**, 654). Pyridazine smells like pyridine, forms soluble salts with acids, and combines with $AuCl_3$, $HgCl_2$, etc.

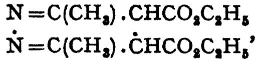
On treating the corresponding pyridazones by method 2 we obtain: 3-**Methyl-,** 3-**Phenyl-,** 5,3-**Methyl-phenyl-pyridazine,** b.p. 214°, m.p. 103° (b.p. 332°, m.p. 95°). 3,6-**Methylphenylpyridazine,** m.p. 103°, 3,6-**Diphenylpyridazine,** m.p. 222°, 3,4,6-**Triphenylpyridazine,** m.p. 171°, from 1,4-diketones by method 1 (see above).

3,6-**Dimethylpyridazine,** m.p. 32°, b.p. 215°, very hygroscopic, is formed from its dicarboxylic acid (B. **37**, 4362). 3-Methylpyridazine condenses, like quinaldine, with benzaldehyde and phthalic acid anhydride.

Pyridazine-3-**carboxylic acid** is obtained from 3-hydroxyphenylpyridazine (method 2) by oxidation with permanganate (B. **32**, 395). 6-**Phenylpyridazine-**3-**carboxylic acid,** m.p. 131°, from 3,6-methylphenylpyridazine with dilute nitric acid (B. **36**, 491). 3,6-**Dimethylpyridazine-**4,5-**dicarboxylic ester,** m.p. 56°, from its dihydro-derivative with nitrous acid. **Pyridazine-**4,5-**dicarboxylic acid,** m.p. 213° with dec., from phthalazine. **Pyridazinetetracarboxylic acid,** from phenazone (see above). 4-**Phenylpyridazine-**5,6-**dicarboxylic acid,** 4-**phenylcinnolinic acid,** m.p. 221°, from 4-phenylcinnoline (see below).

Dihydro-pyridazines are obtained from 1,4-diketones, and hydrazines often with, or instead of, the expected *N*-aminopyrroles (see method 1 for pyridazines). **1-Phenyl-3-methyldihydropyridazine,** m.p. 197° with dec., from lævulinic acid aldehyde with phenylhydrazine (B. **31,** 45). 3,4,6-**Triphenyldihydropyridazine,** m.p. 187°, from desyl-acetophenone with hydrazine, passes, on heating, or treating with chromic acid, into the corresponding pyridazine. 1,3,4,6-**Tetraphenyl-dihydropyridazine,** $C_4H_2(C_6H_5)_4N_2$, m.p. 149°, from desyl-acetophenone and phenylhydrazine, yields, on dry distillation, 1,3,4-triphenylpyrazole (A. **289,** 310).

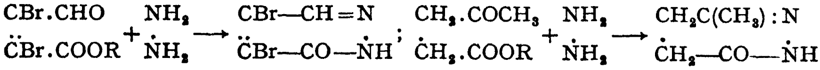
3,6-**Dimethyldihydropyridazinedicarboxylic ester,**



$$\begin{array}{l}N=C(CH_3).CHCO_2C_2H_5\\ \dot{N}=C(CH_3).\dot{C}HCO_2C_2H_5\end{array},$$

is formed from diaceto-succinic acid ester with hydrazine hydrate in alcoholic solution, and with a second molecule of hydrazine yields the cyclo-hydrazide of the acid (B. **36,** 497; **37,** 91).

Keto-dihydro-pyridazines or pyridazones, and keto-tetrahydro-pyridazines or pyridazinones, are formed from 1,4-keto-carboxylic esters with hydrazine hydrate or mono-substituted hydrazines, and must therefore be regarded as ring homologues of the pyrazolones:



$$\begin{array}{l}CBr.CHO\\ \ddot{C}Br.COOR\end{array} + \begin{array}{l}NH_2\\ \dot{N}H_2\end{array} \longrightarrow \begin{array}{l}CBr{-}\dot{C}H{=}N\\ \ddot{C}Br{-}CO{-}\dot{N}H\end{array};\quad \begin{array}{l}CH_2.COCH_3\\ \dot{C}H_2.COOR\end{array} + \begin{array}{l}NH_2\\ \dot{N}H_2\end{array} \longrightarrow \begin{array}{l}CH_2C(CH_3):N\\ \dot{C}H_2{-}CO{-}\dot{N}H\end{array}$$

The pyridazinones are easily oxidized to pyridazones by bromine. With $POCl_3$ the pyridazones give chloropyridazines, the chlorine atom of which is easily replaced.

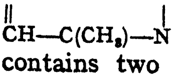
Pyridazones.—**Pyridazone,** $C_4H_4ON_2$, m.p. 104°, is formed from its carboxylic acid, obtained by the oxidation of pyridazinone-3-carboxylic acid (see below) with bromine (B. **42,** 657). **Dibromo-pyridazone,** m.p. 224°, from mucobromic acid with hydrazin (see above).

3-**Methyl-pyridazone,** m.p. 143°, 3-**Phenyl-pyridazone,** m.p. 202°, 5,3-**Methyl-phenyl-pyridazone,** m.p. 190°, 1-**Phenyl-3-methyl-pyridazone,** m.p. 82°, from the corresponding pyridazinones with bromine (B. **34,** 4227, etc.).

Pyridazinones.—**Pyridazinone,** $C_4H_6ON_2$, b.p. 170°, is formed by splitting off CO_2 from **pyridazinone-3-carboxylic acid,** $C_4H_5ON_2.CO_2H$, m.p. 198°, the condensation product of hydrazine with α-keto-glutaric acid (B. **28,** R. 239; **42,** 655).

Pyridazinone is readily decomposed by boiling alkalies, with the splitting off of hydrazine. 3-**Methylpyridazinone,** melting at 94°, and 3-**Phenylpyridazinone,** melting at 149°, are prepared from lævulinic ester and benzoyl propionic ester. 3-**Phenyl-pyridazinone-5-carboxylic ester,** melting at 156°, is obtained from benzoyl*iso*succinic acid ester with hydrazine hydrate (B. **28,** R. 68); 5,3-**methylphenylpyridazinone,** m.p. 157°, from benzoyl *iso*butyric acid with hydrazine (B. **34,** 4230).

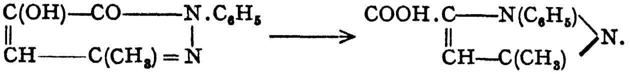
1-**Phenyl-3-methylpyridazinone,** $C_4H_4(CH_3)ON_2C_6H_5$, melting at 107° and boiling at 340°–350°, yields 1-**Phenyl-3-methylpyridazone,**



$$\begin{array}{lcl}CH{-}CO & \text{———} & N.C_6H_5\\ \| & & |\\ CH{-}C(CH_3) & {-} & N\end{array},$$

on treatment with PCl_5 and ice-water. It contains two atoms less of hydrogen. It melts at 82°. *Phenyl-*

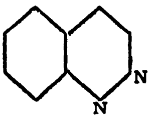
methylchlorpyridazone is formed at the same time, and can be converted by $NaOC_2H_5$ into *ethoxy-phenyl-methyl-pyridazone.* This on saponification becomes *oxyphenylmethylpyridazone,* which undergoes rearrangement into 1-phenyl-3-methylpyrazole-5-carboxylic acid on being heated to 170° with hydrochloric acid (p. 83):



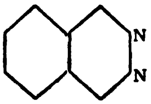
$$\begin{array}{l} C(OH)\text{—}CO\text{——}N.C_6H_5 \\ \| \qquad\qquad\qquad | \\ CH\text{——}C(CH_3)=N \end{array} \longrightarrow \begin{array}{l} COOH.C\text{——}N(C_6H_5) \\ \| \\ CH\text{—}C(CH_3) \end{array} \!\!>\! N.$$

Maleïc Acid Hydrazide, $\begin{array}{l} CH\text{—}CO\text{—}NH \\ \| \qquad\quad | \\ CH\text{—}CO\text{—}NH \end{array}$, melting above 250°, is *diketotetrahydropyridazine,* which is formed, together with the isomeric *N*-amino-maleïnimide, from maleïc anhydride and hydrazine (B. **28,** R. 429). *Diketohexahydropyridazines,* or *orthodiketopiperazines,* are cyclic hydrazides of the succinic acid series, which are produced on heating the chlorides of these acids with the hydrazine hydrochlorides: ***N*-Phenylhexahydropyridazinedione,** $\begin{array}{l} CH_2\text{—}CO\text{—}N.C_6H_5 \\ | \qquad\qquad | \\ CH_2\text{—}CO\text{—}NH \end{array}$.

II. *Benzorthodiazines.*—There are two isomeric benzorthodiazines, depending upon whether the benzene ring attaches itself to the C-atom (3) and (4) or (4) and (5) of orthodiazine. The **cinnolines** and **phthalazines** correspond to these two isomerides:

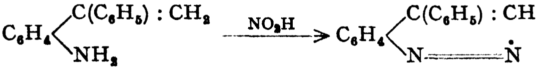


Cinnoline



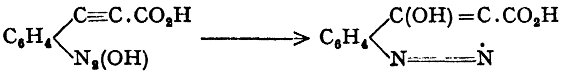
Phthalazine.

Cinnolines are formed by the action of nitrous acid upon *o*-aminostyrenes (B. **17,** 722; **42,** 1315):



$$C_6H_4\!\begin{array}{l} \diagup C(C_6H_5):CH_2 \\ \diagdown NH_2 \end{array} \xrightarrow{NO_2H} C_6H_4\!\begin{array}{l} \diagup C(C_6H_5):CH \\ \diagdown N\text{====}N \end{array}$$

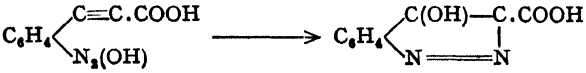
Similarly, hydroxycinnolinecarboxylic acid is obtained from *o*-phenylpropiolic acid diazonium chloride on heating with water:



$$C_6H_4\!\begin{array}{l} \diagup C\equiv C.CO_2H \\ \diagdown N_2(OH) \end{array} \longrightarrow C_6H_4\!\begin{array}{l} \diagup C(OH)=C.CO_2H \\ \diagdown N\text{====}N \end{array}$$

Cinnoline, $C_6H_4\!\begin{array}{l} \diagup CH=CH \\ \qquad\quad | \\ \diagdown N\text{===}N \end{array}$, melting at 39°, is a strong base. It is poisonous. Its *iodomethylate* melts at 168°.

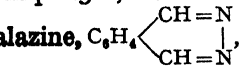
All the cinnoline derivatives known at present have been obtained from **hydroxycinnolinecarboxylic acid,** $C_6H_4[C_2N_2(OH)(COOH)]$, melting at 260°, which is produced on digesting *o*-phenylpropiolic acid diazochloride with water:

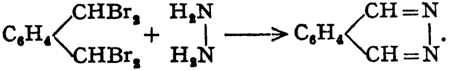


$$C_6H_4\!\begin{array}{l} \diagup C\equiv C.COOH \\ \diagdown N_2(OH) \end{array} \longrightarrow C_6H_4\!\begin{array}{l} \diagup C(OH)\text{—}C.COOH \\ \qquad\qquad\quad | \\ \diagdown N\text{====}N \end{array}$$

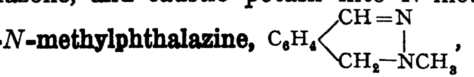
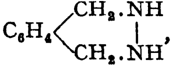
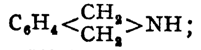
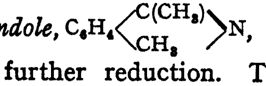
The acid loses CO_2 and becomes **hydroxycinnoline,** $C_8H_5N_2(OH)$, melting at 225°. PCl_5 converts this into **chlorocinnoline,** $C_8H_5N_2Cl$, the chlorine atom of which may be easily replaced by OH, OC_2H_5, NHC_6H_5, etc. Iron filings and sulphuric acid reduce chlorocinnoline to **dihydrocinnoline,** $C_6H_4(C_2H_4N_2)$, melting at 88°, which mercuric oxide oxidizes to cinnoline (B. **25,** 2847; **30,** 521).

4-**Phenylcinnoline** (see above), sulphur yellow crystals, m.p. 67°, is formed from *o*-amino-diphenyl ethylene with nitrous acid; $KMnO_4$ oxidizes it to 4-phenyl-pyridazine-5,6-dicarboxylic acid (B. **42,** 1315). 4-**Methylcinnolinecarboxylic acid,** $CO_2HC_6H_3[C_2HN_2(CH_3)]$, yellow crystals, m.p. 230°, from *o*-amino-propenyl benzoic acid (B. **17,** 722).

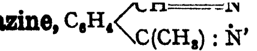
Phthalazine,  $C_6H_4\left\langle\begin{array}{l}CH=N\\ \quad|\\ CH=N\end{array}\right.$, melting at 91° and boiling at 316° (its hydrochloride melts at 231°), is produced when a hydrazine solution acts upon ω-tetrachlor-, or, better, tetrabrom-*o*-xylene:



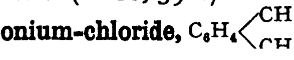
$$C_6H_4\left\langle\begin{array}{l}CHBr_2\\ CHBr_2\end{array}\right. + \begin{array}{l}H_2N\\ \ |\\ H_2N\end{array} \longrightarrow C_6H_4\left\langle\begin{array}{l}CH=N\\ \quad\ |\\ CH=N\end{array}\right. .$$

Also from chloro-phthalazine, by reduction with phosphorus and HI (B. **30,** 3024; **36,** 3377). Phthalazine and methyl iodide form an *iodomethylate,* $C_8H_6N_2.ICH_3$, melting at 235°–240°, which silver oxide converts into *N*-methylphthalazone, and caustic potash into *N*-methyl-phthalazone and **dihydro-*N*-methylphthalazine,**  $C_6H_4\left\langle\begin{array}{l}CH=N\\ \quad\ |\\ CH_2-NCH_3\end{array}\right.$, which oxidizes very rapidly in the air to *N*-methylphthalazone (see the allied rearrangements of the alkyl quinolinium iodides). Sodium amalgam reduces phthalazine to **tetrahydrophthalazine,**  $C_6H_4\left\langle\begin{array}{l}CH_2.NH\\ \quad\ |\\ CH_2.NH\end{array}\right.$, while with zinc dust and hydrochloric acid the product is *o*-xylylene diamine, $C_6H_4(CH_2NH_2)_2$ (B. **26,** 2210; **28,** 1830, 2210). Alkaline permanganate solution oxidizes phthalazine to pyridazine-4,5-dicarboxylic acid (B. **36,** 3378). **Chloro-phthalazine,** $C_6H_4(C_2HClN_2)$, melting at 113°, as well as **methyl-, propyl-,** and *iso***butyl-chlorophthalazine,** melting at 130° and 67° (the third being an oil), result from the action of $POCl_3$ upon phthalazone and alkylic phthalazones. The reduction of these chlorides leads to derivatives of *iso*indole. Thus, chlorophthalazine forms *dihydro*-iso*indole,*  $C_6H_4<\begin{array}{l}CH_2\\ CH_2\end{array}>NH$; and methyl chlorophthalazine, *methyl* iso*indole,*  $C_6H_4\left\langle\begin{array}{l}C(CH_3)\\ CH_2\end{array}\right\rangle N$, which yields dihydromethyl-*iso*indole upon further reduction. The homologues behave similarly (B. **29,** 1434).

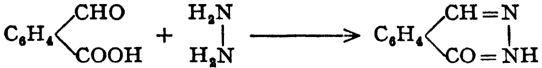
Careful reduction with P and HI, on the other hand, reduces the chloro-phthalazines only down to phthalazines (B. **30,** 3022; **32,** 2014).

Methylphthalazine,  $C_6H_4\left\langle\begin{array}{l}CH\!=\!=\!=\!N\\ C(CH_3):N\end{array}\right.$, m.p. 74°, like quinaldine, condenses with phthalic acid anhydride, chloral, and benzaldehyde to $(C_8H_5N_2)C_8H:C_2O_2C_6H_4$, $(C_8H_5N_2)CH_2.CH(OH)CCl_3$, $(C_8H_5N_2)CH:CHC_6H_5$ (B. **30,** 3033). **Ethylphthalazine,** $C_8H_5N_2(C_2H_5)$, m.p. 23°, b.p.$_{16}$ 190°, from ethyl chloro-phthalazine.

Phenyl- and **Benzyl-phthalazine,** m.p. 142° and 82°, from the corresponding phthalazones (B. **38,** 3918).

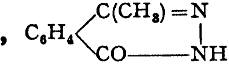
N-**Phenyl-phthalazonium-chloride,** 
$C_6H_4\left\langle\begin{matrix}CH=N\\CH-N(Cl)C_6H_5\end{matrix}\right.$, m.p. 107°, is formed by the condensation of *o*-phthal-aldehyde with phenylhydrazine chloride. With alkalies it passes into *N*-**phenyl-1-hydroxy-dihydro-phthalazine,** m.p. 129°, which, with HCl, regenerates phenylphthalazonium chloride (A. **347,** 114).

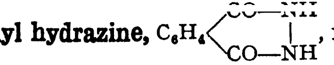
Ketodihydrophthalazines, phthalazones, have been obtained from aromatic *o*-aldehydo- and ketone carboxylic acids by means of the hydrazines:

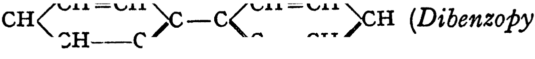

$$C_6H_4\left\langle\begin{matrix}CHO\\COOH\end{matrix}\right. + \begin{matrix}H_2N\\|\\H_2N\end{matrix} \longrightarrow C_6H_4\left\langle\begin{matrix}CH=N\\|\\CO=NH\end{matrix}\right.$$

Phthalaldehydic Acid. Phthalazone.

Phthalazone, $C_8H_6ON_2$, melting at 183° and boiling at 337°, combines with alcoholic potash to *potassium-phthalazone,* $C_8H_5ON_2K$. It can be obtained from phthalazone carboxylic acid, the condensation product of phthalazonic acid with hydrazine (B. **33,** 2808). Acetyl chloride converts it into N-*acetyl-phthalazone,* while methyl iodide converts it into phthalazine iodomethylate.

C-**Methyl phthalazone,** 
$C_6H_4\left\langle\begin{matrix}C(CH_3)=N\\|\\CO——NH\end{matrix}\right.$, melting at 220° and boiling at 348°, is obtained from *o*-acetophenone carboxylic acid (B. **26,** 524, 535). *C*-**Ethyl, Propyl-,** *iso***Butyl-,** and **Benzyl phthalazone** melt at 169°, 156°, 113°, and 152° (B. **29,** 1434).

The cyclic hydrazides of the *o*-phthalic acids are *diketophthalazines.* They correspond to the orthopiperazones, and can therefore be designated benzorthopiperazones. **Phthalyl hydrazine,** 
$C_6H_4\left\langle\begin{matrix}CO—NH\\|\\CO—NH\end{matrix}\right.$, melting beyond 250°, results from the action of hydrazine upon phthalic ester, chloride, or anhydride (J. pr. Ch. [2], **52,** 447; **54,** 66). **Phthalyl phenyl-hydrazine** (II. 357) results when phthalyl phenyl-hydrazide is heated (B. **28,** R. 429).

III. **Phenazone,** 
$CH\left\langle\begin{matrix}CH=CH\\CH——C\end{matrix}\right\rangle C—C\left\langle\begin{matrix}CH=CH\\C——CH\end{matrix}\right\rangle CH$ (*Dibenzopyridazine*), is isomeric with phenazine. It consists of yellow needles, melting at 156°. When o_2-dinitrodiphenyl is reduced electrolytically or with sodium amalgam and methyl alcohol, an intramolecular formation of the azo-group occurs:

Intermediate products formed are phenazone dioxide and phenazone monoxide; phenazone oxide (m.p. 139°) is also easily formed from o_2-dinitrodiphenyl with sodium sulphide. It is reduced to phenazone by stannous chloride (B. **37,** 24). Phenazone is also produced by heating diphenyl-o_2-dihydrazine with HCl to 150°. Reduction of phenazone with HCl and tin produces **dihydrophenazone,** $C_{12}H_8(N_2H_2)$

(B. **24**, 3083). Phenazone is a base, which combines with alkyl haloids (B. **37**, 25). The relations of phenazone to orthodiazine or pyridazine become evident from its oxidation to pyridazine tetracarboxylic acid by potassium permanganate. **Tolazone,** $(C_7H_6)_2N_2$, melting at 187°, is prepared from *o*-dinitroditolyl (B. **26**, 2239).

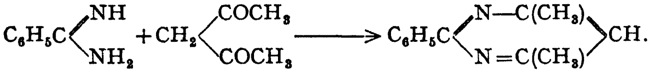
3,6-**Dimethyl-phenazone,** m.p. 188°; 3,6-**Diamino-phenazone,** m.p. 265° (B. **37**, 23).

Substances containing a combined pyridazine and triazole ring have been obtained by the condensation of *N*-amino-triazole with 1,3-diketones and *β*-ketonic acid esters (B. **42**, 2594).

B. META-DIAZINES.

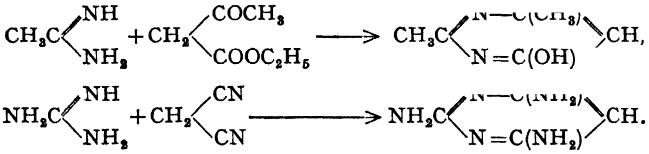
I. *Pyrimidines.*—Pyrimidines or meta-diazines are the analogues of the glyoxalines, and can, like these, be regarded as cyclic amidines. Among the pyramidines we must also reckon purine and its derivatives, containing a twin nucleus of pyrimidine and glyoxaline. The purine bodies, owing to their relations with uric acid and the ureides of the malonic acid series, were mostly dealt with in Vol. I.

Pyrimidines are formed: (1) From carboxylic acid amidines with 1,3-diketones (Pinner, B. **26**, 2125):



$$C_6H_5C\begin{cases}NH\\NH_2\end{cases}+CH_2\begin{cases}COCH_3\\COCH_3\end{cases}\longrightarrow C_6H_5C\begin{cases}N—C(CH_3)\\N=C(CH_3)\end{cases}CH.$$

Amidines with *β*-aldehydic and *β*-ketonic acid esters produce oxy-pyrimidines, and with cyanacetic acid ester aminohydroxypyrimidines. Instead of the amidines, urea, thio-urea, and guanidine may be employed, giving dioxy-pyrimidines (uracils), amino-oxy- and diamino-oxy-pyrimidines, etc., some of which were described in Vol. I. as products of the purine group—*e.g.*:

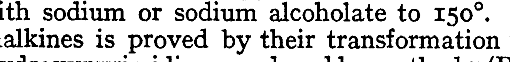


$$CH_3C\begin{cases}NH\\NH_2\end{cases}+CH_2\begin{cases}COCH_3\\COOC_2H_5\end{cases}\longrightarrow CH_3C\begin{cases}N—C(CH_3)\\N=C(OH)\end{cases}CH,$$

$$NH_2C\begin{cases}NH\\NH_2\end{cases}+CH_2\begin{cases}CN\\CN\end{cases}\longrightarrow NH_2C\begin{cases}N—C(NH_2)\\N=C(NH_2)\end{cases}CH.$$

The hydroxypyrimidines, with $POCl_3$, produce chlorinated pyrimidines, which, on boiling with zinc dust and water, are easily reduced to pyrimidines.

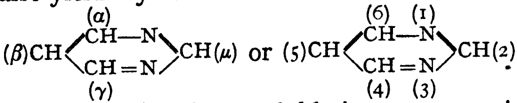
(2) *Nitriles* (cyanalkyls) produce amino-pyrimidines, so-called cyanalkines, on heating with sodium or sodium alcoholate to 150°. The structure of the cyanalkines is proved by their transformation with nitrous acid into the hydroxypyrimidines produced by method 1 (B. **22**, R. 327; C. 1906, I. 941):



$$\begin{matrix}CH_3\\ \dot{N}=C(NH_2)—\dot{C}H\end{matrix}\longrightarrow\begin{matrix}CH_3C=N—CCH_3\\ \dot{N}=C(OH)—\dot{C}H\end{matrix}$$

Intermediate products occur in the formation of cyanalkines in the shape of imines of *β*-ketonic acid nitriles—*e.g.*, $CH_3C(:NH).CH_2CN$

(see Vol. I.), which combine with a third molecule of the nitrile to form imino-pyrimidines. The mixture of two alkyl cyanides with Na or Na alcoholate also yields cyanalkines.

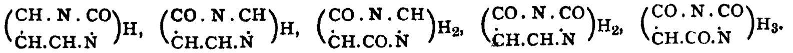
Pyrimidine,  m.p. 21°, b.p. 124°, a base of narcotic odour, soluble in water, precipitated by sublimate. It is formed from pyrimidine-α-carboxylic acid by dry distillation, and from tri- and tetra-chloro-pyrimidine by boiling with zinc dust and water (B. **33,** 3366; **34,** 4178). Similarly, by reduction of chlorinated pyrimidines, the following have been obtained:

Alkylpyrimidines.—**Methylpyrimidines,** α- b.p. 142°; β- m.p. 30°, b.p. 152°; μ- b.p. 138°. **Dimethylpyrimidines,** αβ- m.p. 3°, b.p. 177°; αγ- m.p. 25°, b.p. 159°; αμ- b.p. 146°; **α-Methyl-β-ethylpyrimidine,** b.p. 193°; **α-Methyl-μ-phenylpyrimidine,** m.p. 22°, b.p. 279°; **β-Methyl-αμ-diethylpyrimidine** (*Cyanoconiine*). b.p. 205°: a base acting like coniine (B. **22,** R. 328; **34,** 2825, 3956; **35,** 1575; **36,** 1915; **37,** 3638; **38,** 3394); **αγ-Dimethyl-μ-phenylpyrimidine,** m.p. 83°, b.p. 276°, from benzamidine and acetylacetone (see p. 274).

The methyl groups adjoining the N-atoms, as in the case of picoline, quinaldine, etc., may be condensed with benzaldehyde to P.[α]CH:-CHC_6H_5, P.[αγ]$(CH : CHC_6H_5)_2$, etc. (B. **36,** 3383). The α-methyl-pyrimidine, which results with special ease from methyl-uracil, is split up by reduction with Na and alcohol to αγ-diamino-butane (B. **36,** 1924).

Carboxylic acids are produced from methyl-pyrimidines by oxidation with $KMnO_4$; carboxyls adjoining the N-atoms are easily detached. **Pyrimidine-α-carboxylic acid** is obtained from α-methyl-pyrimidine; β- and **γ-methylpyrimidine-α-carboxylic acids** from αβ- and αγ-dimethylpyrimidines together with the αγ-dicarboxylic acid in the latter case (B. **34,** 2825, 3956). **αβ-Pyrimidine-dicarboxylic acid** is formed from quinazoline (benzo-pyrimidine) by oxidation with $KMnO_4$, and on heating gives **pyrimidine-β-carboxylic acid** (B. **37,** 3647).

Hydroxypyrimidines possess simultaneously a phenol and a basic character, and are also desmotropic with the keto-derivatives of hydrogenated pyrimidines. The desmotropy can be generally expressed by the following formulæ:



$$\left(\begin{matrix}CH.N.CO\\ CH.CH.N\end{matrix}\right)H,\ \left(\begin{matrix}CO.N.CH\\ CH.CH.N\end{matrix}\right)H,\ \left(\begin{matrix}CO.N.CH\\ CH.CO.N\end{matrix}\right)H_2,\ \left(\begin{matrix}CO.N.CO\\ CH.CH.N\end{matrix}\right)H_2,\ \left(\begin{matrix}CO.N.CO\\ CH.CO.N\end{matrix}\right)H_3.$$

These formulæ are to indicate that the H-atoms can be linked to the O, N, or C-atoms. Similar desmotropy is also shown by the amino- and the aminohydroxypyrimidines. This group must therefore be taken to include the ureides, thioureides, and guanides of the β-ketonic acids (uracils, etc.), and of the malonic acid series (barbituric acid, etc.).

Monoxy-pyrimidines.—**α-Hydroxypyrimidine, α-pyrimidone,** m.p. 165°, from αμ-dichloro-pyrimidine under the action of concentrated HI and red phosphorus (C. 1907, II. 1529). **μ-Methyl-α-hydroxypyrimidine,** m.p. 212°, from acetamidine and formyl-acetic ester (B. **37,** 3639). **μ-Phenyl-α-hydroxypyrimidine,** m.p. 208°, b.p.$_{30}$ 260°–263°, from its carboxylic acid, the esters of which (m.p. 214°) result from benzamidine or benzamidoxime with dicarboxy-glutaconic acid ester (B. **30,** 1488, 1564). **μα-Dimethyl-γ-hydroxypyrimidine,** m.p. 192°, from aceto-acetic ester and acetamidine, or from cyano-methine (see below) and HNO_2. **αγ-Dimethyl-μ-hydroxypyrimidine,** m.p. 198°, from acetyl-acetone and urea (B. **34,** 3956; **43,** 1126). **α,μ-Methyl-phenyl-γ-hydroxypyrimidine,** m.p. 216° (B. **35,** 1575).

Dihydroxypyrimidines or *uracils* from β-ketonic acid esters and urea, as well as amino-oxypyrimidines with HNO_2, or by heating with HCl, or from hydro-uracils with bromine (see Vol. I.: Uracile, methyl-uracile). Also **α,β-Dimethyl- γ,μ-dihydroxypyrimidine,** m.p. 290°, **α,β-Methyl-ethyl-γ,μ-dihydroxypyrimidine** (B. **36,** 1915), etc.

Trioxy-pyrimidines are represented by barbituric acid or malonyl urea.

Amino-pyrimidines are found as cyanalkines: **Cyano-methine, μα-dimethyl-γ-aminopyrimidine,** m.p. 180°. **Cyanethine, μα-diethyl-β-methyl-γ-aminopyrimidine,** m.p. 189°. **Cyanobenzyline, μα-dibenzyl-β-phenyl-γ-aminopyrimidine,** m.p. 106° (B. **29,** R. 787).

2- and 6-**Amino-pyrimidine** and 2,6-**diamino-pyrimidine** are obtained by reducing their halogen substitution products (B. **34,** 3362; **36,** 2227).

αγμ-Triamino-pyrimidine, m.p. 246°, from αγμ-trichloro-pyrimidine with NH_3 at 200°, and from guanidine and malononitrile by means of sodium ethylate (B. **37,** 4544). With HNO_2 it gives nitroso-amino-pyrimidine, which may be reduced to **μαβγ-tetramino-pyrimidine. αβγ-Triamino-pyrimidine,** heated with formic acid, yields *adenine* (Vol. I.). It is formed by oxidation with H_2O_2 from **αβγ-triamino-μ-thiopyrimidine,** and the latter from **αγ-diamino-μ-thiopyrimidine,** which itself is obtained synthetically from thiourea and malonitrile. Similarly, thiourea and cyanacetic ester give **αγ-aminohydroxy-μ-thio-pyrimidine** or **αβ-diamino-γ-oxy-μ-thiopyrimidine,** which, by condensation with formic acid and oxidative rejection of the SH group, gives *hypoxanthine* (Vol. I.) (A. **331,** 64).

Aminohydroxypyrimidines are produced: (1) From β-ketonic acid esters with guanidine—*e.g.*, **αβ-dimethyl-** and **αβ-methylethyl-γ-hydroxy-μ-aminopyrimidine** from guanidine with methyl- and with ethyl aceto-acetic ester respectively (B. **34,** 2825; **36,** 1915). (2) From amidines with cyanacetic ester and sodium ethylate—*e.g.*, **μ-methyl-** and **μ-phenyl-α-hydroxy-γ-aminopyrimidine** (B. **37,** 2267; C. 1902, II. 1229).

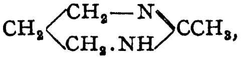
α-Amino-γμ-dihydroxypyrimidine, by condensation of cyanacetyl urea with alkali (B. **41,** 522). **αβ-Diamino-γμ-dihydroxy-** and **β-amino-αγμ-trihydroxypyrimidine** (uramile) are used for building up urea (Vol. I.).

Chloro-pyrimidines are formed by the action of $POCl_3$ upon the oxy-pyrimidines, and are important intermediate products, since the Cl-atoms are easily replaced by NH_2, OR, SH, or H.

μ-Chloro-αγ-dimethylpyrimidine, m.p. 38°, b.p. 223°; **γ-chloro-αμ-dimethyl-** and **-αμ-methylphenylpyrimidine** (B. **34,** 3956; **35,** 1575). **γμ-Dichloro-α-methyl-, αβ-dimethyl-** and **αβ-methylethyl-pyrimidine,** m.p. 47°, b.p. 219°; m.p. 71°; m.p. 39° respectively (B. **34,** 2825; **36,** 1915). **αγμ-Trichloro-pyrimidine,** m.p. 21°, b.p. 213°, from barbituric acid (B. **37,** 3657); **αβγμ-tetra-chloro-pyrimidine,** m.p. 70°, from dialuric acid (B. **34,** 4176); with NH_3, trichloropyrimidine, according to the temperature, gives aminodichloropyrimidine, diaminochloropyrimidine, or triaminopyrimidine (see above). **μ-Phenyl-β-chloro-pyrimidine,** m.p. 96°, and **μ-phenyl-β-bromo-pyrimidine,** m.p. 104°, are obtained from their carboxylic acids, resulting from muco-chloric and muco-bromic acid with benzamidine (B. **35,** 3167).

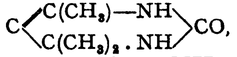
Hydro-pyrimidines.—Tetrahydro-pyrimidines are formed from 1,3-diamines with carboxylic acids or from 1,3-dibromides with carboxylic amidines.

μ-Methyl - tetrahydro - pyrimidine,



$CH_2\left\langle\begin{array}{l}CH_2—N\\CH_2.NH\end{array}\right\rangle CCH_3$, m.p. 73°, b.p.$_{20}$ 120°–126°, from trimethylene diamine with acetic acid. **αγμ-Trimethyl tetrahydro-pyrimidine,** *cis*-form m.p. 73°, *trans*-form m.p. 102°, from the two forms of αγ-diamino-butane with acetic acid (B. **32,** 1191; **36,** 334). **μ-Phenyltetrahydro-pyrimidine** from trimethylene bromide and benzamidine (B. **26,** 2122). **μ-Phenyl-β-ketotetrahydropyrimidine,** m.p. 91°, from diamino-acetone and benzoyl-chloride (B. **25,** 1564; **27,** 277).

α,γ,γ - Trimethyl - μ - ketotetrahydropyrimidine,



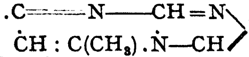
$C\left\langle\begin{array}{l}C(CH_3)—NH\\C(CH_3)_2.NH\end{array}\right\rangle CO$, m.p. 194°, from the urea derivative of diacetoneamine, NH_2-$CONHC(CH_3)_2.CH_2COCH_3$ (B. **32,** 3156).

***N*-Diphenyl-hexahydro-pyrimidine,** $CH_2N_2(C_6H_5)_2(CH_2)_3$, m.p. 87°, from trimethylene-dianiline with formaldehyde (B. **32,** 2253).

The desmotropic forms of mono-, di-, and trioxy-pyrimidines, amino-pyrimidine, and amino-oxy-pyrimidine are *keto-* and *amino-derivatives* of di-, tetra-, and hexahydro-pyrimidines.

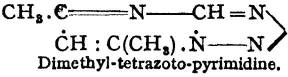
Purine and its derivatives contain, as already mentioned, a twin ring of pyrimidine and glyoxaline. The purines have mostly been built up out of αβ-diamino- or oxy-amino-pyrimidines (see above).

A similar hetero-twin ring is contained in the so-called *alloxazines* (B. **32,** 1650, etc.), resulting from alloxan and *o*-phenylene diamines (B. **32,** 1650, etc.):



$\begin{array}{l}N=CH—C—N=\\ \dot{C}H=N—\ddot{C}—NH\end{array}\Big\rangle CH$

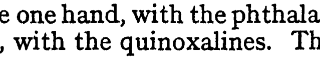
Purine.



$\begin{array}{l}N——CO—C=N\\ \dot{C}O—NH—\dot{C}=N\end{array}\Big\rangle C_6H_4.$

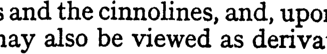
Alloxazine.

Twin-ring combinations of pyrimidine with *sym*-triazole and tetrazole have been obtained by the condensation of *C*-amino-triazole and *C*-aminotetrazole with 1,3-diketones or β-ketone carboxylic esters (B. **42,** 4429, 4638):



$\begin{array}{l}CH_3.C=——N——CH=N\\ \quad\dot{C}H : C(CH_3).\dot{N}—CH\end{array}\Big\rangle N$

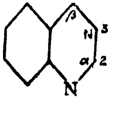
Dimethyl-triazo-pyrimidine.



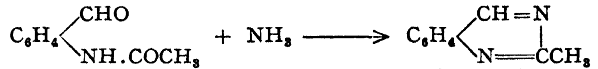
$\begin{array}{l}CH_3.C=——N——CH=N\\ \quad\dot{C}H : C(CH_3).\dot{N}——N\end{array}\Big\rangle N.$

Dimethyl-tetrazoto-pyrimidine.

II. *Quinazolines.*—The benzometadiazines or benzopyrimidines are the *quinazolines,* sometimes called *phenomiazines.* They are metameric, on the one hand, with the phthalazines and the cinnolines, and, upon the other, with the quinoxalines. They may also be viewed as derivatives of the quinolines or *iso*quinolines by the substitution of an azo-ring:



Quinazolines are produced when the acidyl compounds of *o*-amino-benzaldehyde or of *o*-amino-benzoketones are treated with alcoholic ammonia (B. **28,** 279):



$$C_6H_4\left\langle\begin{matrix}CHO\\ NH.COCH_3\end{matrix}\right. + NH_3 \longrightarrow C_6H_4\left\langle\begin{matrix}CH=N\\ \quad\;|\\ N=CCH_3\end{matrix}\right.$$

o-Acetamidobenzaldehyde. *a*-Methyl quinazoline.

Quinazolines are also produced from the dihydroquinazolines by oxidation with potassium ferricyanide (B. **36,** 810).

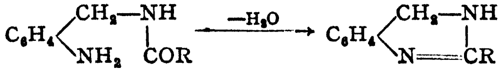
The quinazolines are stable tertiary bases which distil without decomposition. They take up alkyl iodides. Sodium and alcohol reduce them to dihydroquinazolines (B. **26,** 1385). Chromic acid in glacial acetic acid oxidizes the quinazolines, in which the CH-group adjacent to the benzene nucleus is free, to ketodihydroquinazolines (or oxyquinazolines, etc.).

Quinazoline, $C_6H_4\left\{\begin{matrix}CH=N\\ \quad\;|\\ N=CH\end{matrix}\right.$, m.p. 48°, b.p. 243°, from dihydroquinazoline with potassium ferricyanide, and from the condensation product of *o*-nitro-benzaldehyde with formamide by reduction with zinc dust and acetic acid (C. 1906, II. 1372). It combines with methyl iodide; the iodo-methylate with KHO gives *N*-**methyl-quinazolinium hydroxide,** $C_8H_7N_2(CH_3)(OH)$, m.p. 164°, which, on distillation with KHO, is split up into formic acid and *o-amino-benzaldehyde-methylimine,* $NH_2C_6H_4CH:NCH_3$ (B. **37,** 3650). $KMnO_4$ mainly oxidizes quinazoline to *pyrimidine-4,5-dicarboxylic acid* (B. **37,** 3646).

a-**Methylquinazoline,** $C_8H_5(CH_3)N_2$, melts at 35° and boils at 238°; from *o*-acetamino-benzaldehyde or *a*-methyl-dihydro-quinazoline (B. **36,** 810). *a,β*-**Dimethylquinazoline** is an oil boiling at 249°. It is formed when ammonia acts upon *o*-acetaminoacetophenone. *a*-**Phenyl-quinazoline,** $C_8H_5(C_6H_5)N_2$, melting at 101° and boiling above 300°, results when ammonia acts upon *o*-benzoylaminobenzaldehyde, as well as from *o*-aminobenzyl-benzamide instead of the expected dihydro-derivative. *a*-**Methyl-***β*-**phenylquinazoline,** $C_8H_4(CH_3)(C_6H_5)N_2$, melts at 48°. It is obtained from *o*-acetamino-benzophenone. Chromic acid oxidizes it to *β*-**phenyl-quinazoline-***a*-**carboxylic acid.**

Keto-hydro-quinazolines and PCl_5 yield chloro-quinazolines. *a*- and *β*-**Chloro-quinazolines,** melting at 108° and 96°, are obtained from *a*- and *β*-quinazolones. *a*-**Chloro-***β*-**phenylquinazoline,** melting at 113°, is made from phenyl-*a*-quinazolone (B. **29,** 1310). *a,β*-**Dichloro-quinazoline,** melting at 115°, is obtained from benzoylene urea.

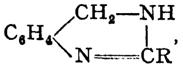
Dihydro-quinazolines, containing the same atomic grouping, $\left.\begin{matrix}-N=\\ -NH\end{matrix}\right\rangle CR$, as the anhydro-bases of the *o*-phenylenediamines, the benziminazoles, are to be regarded as the ring homologues of the latter —as *anhydro-bases* of the *o-aminobenzylamines.* They result by the elimination of water from the acidyl compounds of *o*-aminobenzyl-amine and its substitution products (B. **24,** 3096; **25,** 3037; **27,** R. 74; **29,** R. 1131; **37,** 3644):



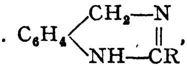
$$C_6H_4\left\langle\begin{matrix}CH_2-NH\\ \qquad\quad|\\ NH_2\quad COR\end{matrix}\right. \xrightarrow{-H_2O} C_6H_4\left\langle\begin{matrix}CH_2-NH\\ \qquad\;|\\ N=CR\end{matrix}\right.$$

The reaction proceeds the same if the acidyl group replaces the aromatic NH_2 residue. Further, the *o*-amino-benzyl-acidylamines can rearrange themselves to *o*-acidylamino-benzylamines (B. **26,** 1891, R. 374). The same anhydro-bases may also be obtained by reducing the corresponding *o*-nitro-benzylamine compounds.

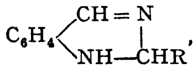
The dihydro-quinazolines are rather strong bases, forming stable salts. Free imine hydrogen in them is readily replaced by alkyls. Like the quinazolines, they yield keto-dihydro-quinazolines upon oxidation. They decompose upon distillation with zinc-dust. Sodium and alcohol reduce them to tetrahydro-quinazolines. It may be noted that three isomeric, hydrogenized dihydro-compounds are possible from each *C*-alkylquinazoline:

I. 

$C_6H_4\begin{cases}CH_2—NH \\ N=\!=CR\end{cases}$,

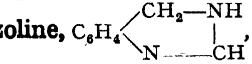
II. 

$C_6H_4\begin{cases}CH_2—N \\ NH—CR\end{cases}$,

III. 

$C_6H_4\begin{cases}CH=N \\ NH—CHR\end{cases}$,

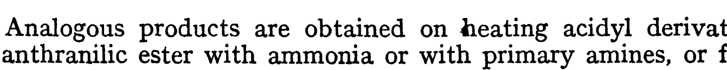
which, adopting the nomenclature of the hydrobenzenes, might be distinguished by the prefixes Δ_1, Δ_2, and Δ_3. Of the dihydro-quinazolines, only Δ_1-dihydro-quinazoline is known.

Δ_1-Dihydro-quinazoline,  $C_6H_4\begin{cases}CH_2—NH \\ N=\!=CH\end{cases}$, melting at 127°, results from the reduction of *o*-nitrobenzyl formamide (B. **24,** 3097); from heating *o*-benzylene diamine with formic acid (B. **37,** 3645); and from the reduction of *α*- and *β*-chloro-quinazoline and *αβ*-dichloro-quinazoline with glacial acetic HI acid (B. **38,** 3559). ***N*-Methyldihydroquinazoline,** m.p. 92°, b.p. 309°, from *o*-amino-benzyl-methylamine with formic acid.

***N*(3)-Phenyldihydroquinazoline,** $C_8H_7(C_6H_5)N_2$, melting at 95°, is prepared from *o*-nitrobenzyl formanilide. Under the name of *orexin* it has been recommended as a stomachic.

***α*-Methyldihydroquinazoline,** $C_8H_7(CH_3)N_2$, is obtained from *o*-aminobenzylacetamide. ***β*-Phenyldihydroquinazoline,** melting at 166°, is produced by reducing *α*-chloro-*β*-phenylquinazoline (B. **29,** 1310).

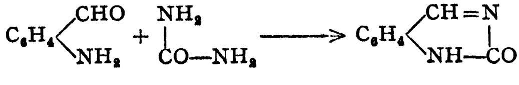
β(4)-*Keto-dihydro-quinazolines, β-quinazolones,* are formed, just like the dihydro-quinazolines, from the acidyl derivatives of *o*-aminobenzamide:



$$C_6H_4\begin{cases}CO—NH_2 \\ NH.COCH_3\end{cases} \text{ or } C_6H_4\begin{cases}CO—NH \\ NH_2 \quad COCH_3\end{cases} \longrightarrow C_6H_4\begin{cases}CO—NH \\ N=\!=C.CH_3\end{cases}$$

Analogous products are obtained on heating acidyl derivatives of anthranilic ester with ammonia or with primary amines, or from anthranilic acid and the amides of fatty acids (C. 1903, I. 1270; 1911, I. 561; B. **27,** R. 516; **28,** R. 783). *β*-Keto-dihydro-quinazolines, as mentioned, are produced, in addition to these synthetic methods, by oxidizing quinazolines and dihydro-quinazolines.

α(2)-*Keto-dihydro-quinazolines, α-quinazolones,* are produced when *o*-amino-benzaldehydes and -benzene ketones are heated with urea B. **29,** 1300):



$$C_6H_4\begin{cases}CHO \\ NH_2\end{cases} + \begin{matrix}NH_2 \\ | \\ CO—NH_2\end{matrix} \longrightarrow C_6H_4\begin{cases}CH=N \\ NH—CO\end{cases}$$

The quinazolones possess both feeble phenol and basic characters, hence can also be regarded as hydroxyquinazolines. They combine with alkyl iodides to *N*-alkyl derivatives of the keto-form. The isomeric *alkoxyquinazolines* are obtained from the *chloroquinazolines.*

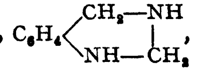
β-Ketodihydroquinazoline, *β-hydroxyquinazoline,* $C_8H_6ON_2$, melting at 214°, is produced from anthranilic acid and formamide (J. pr. Ch. [2], **43,** 215; **51,** 564). Methyl iodide converts it into ***N*-methylketodihydroquinazoline,** $C_8H_5ON_2.CH_3$, melting at 71°.

α-Methyl-β-ketodihydroquinazoline, melting at 232°, is obtained from *o*-acetaminobenzamide or *o*-aminobenzoylacetamide (see above), and also in the oxidation of α-methylquinazoline (B. **28,** 279). **α-Phenyl-β-ketodihydroquinazoline,** $C_8H_5(C_6H_5)NO_2$, melting at 236°, is made from phenylquinazoline or *o*-benzoylaminobenzamide. ***N*-Phenyl-β-ketodihydroquinazoline,** melting at 139°, is obtained by oxidizing *N*-phenyldihydro-quinazoline (B. **24,** 3055; see also B. **28,** 279; C. 1911, I. 326; C. 1906, II. 1124; C. 1899, I. 847).

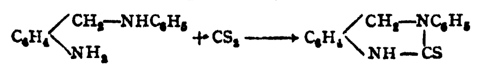
α-Ketodihydroquinazoline, α-Quinazolone, is formed from *o*-aminobenzaldehyde and urea, as well as by oxidizing benzylene-ψ-thiourea with $Ba(MnO_4)_2$. **β-Phenyl-α-ketodihydroquinazoline,** melting at 251°, is prepared from *o*-aminobenzophenone and urea (B. **29,** 1310).

β-Ketodihydroquinazoline-α-carboxylic acid, m.p. 230°, by transposition of cyanoxanilic acid, or action of alcoholic NH_3 upon ethoxalylanthranil. Its nitrile, dicyanamino-benzoyl, by the action of cyanogen upon aqueous anthranilic acid (B. **42,** 3713; C. 1910, I. 748).

Tetrahydro-quinazolines are produced by the reduction of quinazolines, dihydro-quinazolines, and thio-tetrahydro-quinazolines. They also result in the condensation of *o*-aminobenzylamines with aldehydes (J. pr. Ch. [2], **53,** 414; **55,** 356). They may be readily decomposed into benzene ortho-derivatives.

Tetrahydroquinazoline,  $C_6H_4\begin{cases}CH_2-NH\\ NH-CH_2\end{cases}$, is amorphous, and results from the interaction of *o*-aminobenzylamine and formaldehyde, or from dihydro-quinazoline by reduction with Na amalgam (B. **36,** 811), ***N*(3)-Phenyltetrahydroquinazoline,** $C_6H_4(C_2H_5N.C_6H_5)$, melting at 119°, is derived from *o*-aminobenzylaniline and formaldehyde, also from phenyldihydro- and phenylthiotetrahydro-quinazoline (B. **25,** 2858). **α-Phenyltetrahydroquinazoline** melts at 100° (B. **25,** 3033). See B. **29,** 1308, for **β-Phenyltetrahydroquinazoline.** ***N*-Dibenzoyl-α,β-dimethyl tetrahydroquinazoline,** $C_8H_6(CH_3)_2N_2(COC_6H_5)_2$, melts at 155° (B. **26,** 1385).

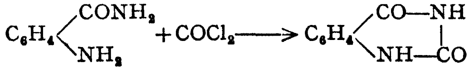
α-Keto- and *thio-tetrahydro-quinazolines* correspond to the cyclic phenylene ureas and -thioureas. They are, like these, produced when $COCl_2$ or CS_2 acts upon *o*-amino-benzylamines, or by the exit of NH_3 or amine from the urea derivatives of the *o*-aminobenzylamines (B. **25,** 2856; **27,** R. 74, etc.):



$$C_6H_4\begin{cases}CH_2-NHC_6H_5\\ NH-CO.NHC_6H_5\end{cases} \text{ or } C_6H_4\begin{cases}CH_2-NC_6H_5\\ NH_2\quad CONHC_6H_5\end{cases} \longrightarrow C_6H_4\begin{cases}CH_2-N.C_6H_5\\ NH-CO\end{cases} (+ NH_2C_6H_5)$$

$$C_6H_4\begin{cases}CH_2-NHC_6H_5\\ NH_2\end{cases} + CS_2 \longrightarrow C_6H_4\begin{cases}CH_2-NC_6H_5\\ NH-CS\end{cases}$$

Diketo-tetahydro-quinazolines are similarly produced from the *o*-amino-benzamides by means of $COCl_2$, $ClCO_2R$, etc., or from urea derivatives of *o*-amino-benzamide or of the anthranilic acids:



$$C_6H_4\left\langle\begin{matrix}CONH_2\\NH_2\end{matrix}\right. + COCl_2 \longrightarrow C_6H_4\left\langle\begin{matrix}CO—NH\\ \vert\\ NH—CO\end{matrix}\right.$$

Keto- and thio-tetrahydro-quinazolines are indifferent bodies. Mention has already been made of their formation from benzometoxazine derivatives, the imino- and thio-cumazones, by heating them with aromatic amines. Oxidants convert them into diketo-tetrahydro-quinazolines, which also result from the oxidation of imino-cumazones (B. **27,** 2420). The diketo-tetrahydro-quinazolines possess acid properties and dissolve only in alkalies. PCl_5 converts them into *dichloro-quinazolines.*

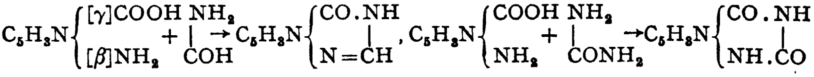
N(3)-**Phenyl-α-ketotetrahydroquinazoline,** $C_8H_7.ON_2.C_6H_5$, melts at 189° (B. **27,** 74). **β-Phenyl-α-ketotetrahydroquinazoline,** melting at 193°, is obtained from *o*-aminobenzohydrol and urea, as well as from the corresponding phenylthiotetrahydroquinazoline. The latter is brominated, and the bromdihydrophenylquinazoline is then converted by soda into ketoquinazoline (B. **29,** 1307).

α-Thiotetrahydroquinazoline, $C_8H_8SN_2$, melts at 211°. ***N*-Phenyl-α-thiotetrahydroquinazoline,** $C_8H_7SN_2.C_6H_5$, melts at 260° (B. **27,** 2432). **β-Phenyl-α-thiotetrahydroquinazoline,** melting at 230°, is obtained from *o*-aminobenzohydrol and hydrosulphocyanic acid (B. **29,** 1305).

Diketotetrahydroquinazoline, Benzoyleneurea, $C_6H_4(C_2O_2N_2H_2)$, melts above 360° and sublimes. ***N*-Phenyldiketotetrahydroquinazoline,** $C_6H_4(C_2O_2NHC_6H_5)$, melts at 272° (B. **27,** 974, 2410, R. 392; compare also B. **30,** 1682).

α-Thio-β-ketotetrahydroquinazoline, $C_6H_4(C_2OSN_2H_2)$, melting at 284°, is prepared from anthranilic ester and hydrosulphocyanic acid (B. **30,** 1098; C. 1897, I. 592).

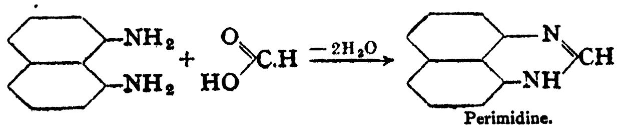
A constitution analogous to that of quinazoline is possessed by the so-called **copazoline,** which contains the pyridine ring instead of the benzo-ring. Derivatives of copazoline are formed from β-amino-*iso*-nicotinic acid, which yields **hydroxycopazoline** with formamide and **dihydroxycopazoline** with urea:



$$C_5H_3N\left\{\begin{matrix}[\gamma]COOH\\ \\ [\beta]NH_2\end{matrix}\right. + \begin{matrix}NH_2\\ \vert\\ COH\end{matrix} \rightarrow C_5H_3N\left\{\begin{matrix}CO.NH\\ \quad\ \vert\\ N=CH\end{matrix}\right., \quad C_5H_3N\left\{\begin{matrix}COOH\\ \\ NH_2\end{matrix}\right. + \begin{matrix}NH_2\\ \vert\\ CONH_2\end{matrix} \rightarrow C_5H_3N\left\{\begin{matrix}CO.NH\\ \quad\ \vert\\ NH.CO\end{matrix}\right.$$

With PCl_5, oxy-copazoline gives **chlorocopazoline,** $C_5H_3N(C_2N_2HCl)$, m.p. 112°, which is reduced by HI to **dihydrocopazoline,** $C_5H_3N(C_2N_2H_4)$, m.p. 145° (B. **35,** 2831).

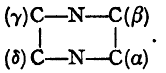
Compounds due to the attachment of a pyrimidine ring at the "peri" position of the naphthalene ring are called perimidines. They correspond to the benziminazoles, and, like these, are formed by the condensation of 1,8-naphthylene diamine with carboxylic acids (A. **365,** 53):



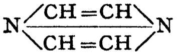
Perimidine.

Perimidine forms green crystals of m.p. about 220°. Similar compounds of the anthracene series have been obtained from α-aminoanthraquinone by transposition with urethane, formamide, etc.

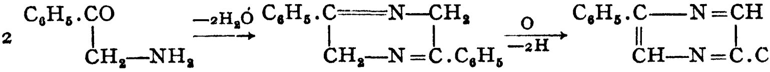
C. PARADIAZINES,



$$\begin{array}{l}(\gamma)C—N—C(\beta)\\ \quad\ |\qquad\quad |\\ (\delta)C—N—C(\alpha)\end{array}.$$

I. Paradiazines are the **pyrazines**, or *piazines*, which can be regarded as pyridines, the methine group of which is substituted in the γ-position by N. It has, however, been suggested that there is a " para-union " of the two N-atoms in the pyrazines, agreeing with the formula  $N\begin{array}{l}\diagup CH=CH\diagdown\\ \diagdown CH=CH\diagup\end{array}N$ (Wolff, B. **26,** 722).

Pyrazines are formed (1) by condensing two molecules of α-aminoaldehydes and α-aminoketones. In this case there is a condensation of two molecules with expulsion of water, forming dihydro-pyrazines, which are oxidized in air to pyrazines (compare B. **41,** 1128):

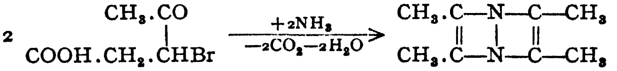


$$2\ \begin{array}{l}C_6H_5.CO\\ \quad|\\ CH_2—NH_2\end{array} \xrightarrow{-2H_2O} \begin{array}{l}C_6H_5.C{=\!=}N—CH_2\\ |\qquad\qquad\quad |\\ CH_2—N=C.C_6H_5\end{array} \xrightarrow[-2H]{O} \begin{array}{l}C_6H_5.C—N=CH\\ \|\qquad\qquad |\\ CH—N=C.C_6H_5\end{array}$$

On account of their relations with α-amino-aldehydes and ketones, the pyrazines are also called " aldines " or " ketines."

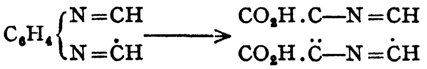
Instead of isolating the amino-ketones, the solution of them obtained in the reduction of *iso*nitroso-ketones can be distilled with the addition of $HgCl_2$ as an oxidizing agent (B. **26,** 1832, 2207).

(2) The synthesis of pyrazines from α-chloro- or bromoketo-compounds and ammonia also depends upon the intermediate formation of α-aminoketones. Thus, β-bromlævulinic acid and ammonia yield tetramethyl-pyrazine, with the evolution of carbon dioxide:



$$2\ \begin{array}{r}CH_3.CO\\ |\\ COOH.CH_2.CHBr\end{array} \xrightarrow[-2CO_2-2H_2O]{+2NH_3} \begin{array}{l}CH_3.C—N—C—CH_3\\ \quad\ \|\quad\ |\quad\ \|\\ CH_3.C—N—C—CH_3\end{array}$$

(3) Pyrazine-*o*-dicarboxylic acids have also been obtained by oxidative disintegration of quinoxaline and its homologues by means of $KMnO_4$ (B. **40,** 4850):

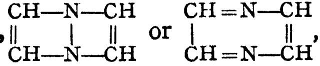


$$C_6H_4\left\{\begin{array}{l}N=CH\\ N=CH\end{array}\right. \longrightarrow \begin{array}{l}CO_2H.C—N=CH\\ CO_2H.C—N=CH\end{array}$$

Pyrazines occur also in the fermentation products of sugar. Thus, α,γ-dimethyl- and trimethyl-pyrazine have been isolated from fusel oil. Pyrazines also result in the action of ammonia upon grape-sugar. In this instance the products are pyrazine, methyl-, and dimethyl pyrazines (B. **30,** 224; J. pr. Ch. [2], **54,** 481).

The pyrazines are feeble bases, which give a neutral reaction with litmus. They form readily dissociated salts with acids. Like the pyridines, they form characteristic compounds with metallic salts—*e.g.*, mercuric chloride, auric chloride, etc.

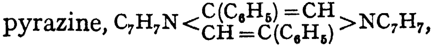
Sodium reduces the pyrazines to piperazines or hexahydropyrazines corresponding to the piperidines. Potassium permanganate oxidizes alkylic pyrazines to pyrazine carboxylic acids, which part with carbon dioxide very readily.

Pyrazine,  $\begin{array}{c}CH—N—CH\\ \| \quad | \quad \|\\ CH—N—CH\end{array}$ or $\begin{array}{c}CH=N—CH\\ | \qquad \|\\ CH=N—CH\end{array}$, melting at 55° and boiling at 115° (B. **27**, R. 396), is a substance smelling like heliotrope and subliming at the ordinary temperature. It is produced when aminoacetaldehyde or aminoacetal (I. 339) is distilled with a sublimate solution, also by eliminating carbon dioxide from the pyrazine carboxylic acids, and upon distilling piperazine with zinc-dust (B. **26**, R. 441).

Methylpyrazine, $C_4H_3(CH_3)N_2$, boiling at 135°, is obtained from its carboxylic acid (B. **28**, R. 551), and constitutes the chief constituent of the bases produced in the action of ammonia upon grape-sugar. **αβ-Dimethylpyrazine,** from diacetyl and ethylene diamine, and from its dicarboxylic acid (see below) (B. **40**, 4855). **α,γ-Dimethylpyrazine,** *Ketine*, $C_4H_2(CH_3)_2N_2$, is an oil boiling at 153°. It is formed in the reduction of *iso*nitrosoacetone, and, together with pyridine bases and other alkylic pyrazines—*e.g.*, **α,γ,δ-methyldiethylpyrazine,** b.p. 179° (B. **24**, 4105; **26**, R. 442)—upon distilling glycerol with ammonium salts.

α,δ-Dimethylpyrazine melts at 48° and boils at 155° (J. pr. Ch. [2], **54**, 492). **Trimethylpyrazine,** boiling at 172°, is produced on heating the bromomethylate of α,γ-dimethylpyrazine (B. **29**, R. 980). **Tetramethylpyrazine,** $C_4(CH_3)_4N_2(+3H_2O)$, melts at 86° (75°) and boils at 190°. It is produced when ammonia acts upon β-bromolævulinic acid (I. 423), or by reducing β-isonitroso-lævulinic acid (B. **25**, 1723).

The methyl-pyrazines, like picoline and quinaldine, can condense with benzaldehyde or chloral with expulsion of water—*e.g.*, $(C_4H_2N_2)[\alpha\gamma](CH:CHC_6H_5)_2$ (B. **38**, 3724).

α,γ-Diphenylpyrazine, $C_4(C_6H_5)_2H_2N_2$, melting at 196°, results from ω-amino-acetophenone, and from *N*-dibenzyldihydro-α,γ-diphenylpyrazine,  $C_7H_7N<\begin{smallmatrix}C(C_6H_5)=CH\\ CH=C(C_6H_5)\end{smallmatrix}>NC_7H_7$, by the loss of toluene (B. **27**, R. 135). The isomeric **α,δ-diphenylpyrazine,** melting at 89°, is similarly formed from *N*-benzyl-dihydro-α,δ-diphenylpyrazine (see below) by the splitting off of toluene. **α,γ-Diphenyl-dimethylpyrazine,** $C_4(C_6H_5)_2(CH_3)_2N_2$, melting at 126°, is prepared from *iso*nitroso-phenylacetone (B. **29**, R. 548), and from its dihydro-compounds (B. **41**, 1150).

Tetraphenylpyrazine, *Tetraphenylaldine*, $C_4(C_6H_5)_4N_2$, melting at 246°, is made by reducing the benzil monoximes or dioximes (B. **27**, 213).

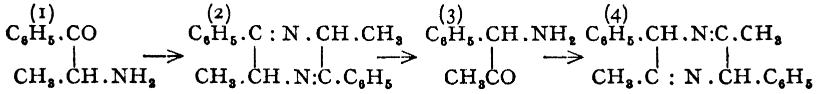
Pyrazine monocarboxylic acid, melting with decomposition at 230°, **pyrazine αγ-dicarboxylic acid,** $C_4H_2(COOH)_2N_2(+2H_2O)$, melting at 256°, and **pyrazine tetracarboxylic acid,** $C_4(COOH)_4N_2$, melting at 205°, etc., result upon oxidizing the methylated pyrazines with potassium permanganate. **Pyrazine-αβ-dicarboxylic acid,** m.p. 193° with dec., and **dimethylpyrazine-αβ-dicarboxylic acid,** m.p. 200° with dec., from quinoxaline and dimethyl-quinoxaline respectively by oxidation (B. **40**, 4850). Consult B. **26**, R. 442, for other pyrazine carboxylic acids.

Dihydro-pyrazines, containing two imine groups, are prepared, together with the isomeric indoles, in the action of anilines upon α-alkylaminoketone derivatives, $RHNCH_2.CO—$, or from α-bromketones and primary amines.

N-**Diphenyl sulphonedihydropyrazine,** $C_6H_5SO_2N<\begin{smallmatrix}CH=CH\\ CH=CH\end{smallmatrix}>NSO_2C_6H_5$, melting at 163°, is obtained from benzenesulphaminoacetal (B. **26,** 98). *N*-**Diphenyl-dihydro-α,γ-diphenylpyrazine,** $C_4H_2(C_6H_5)_2(N.C_6H_5)_2$, melting at 181°, is formed from aniline and phenacyl bromide (p. 248). Different dihydro-pyrazine derivatives, like *N*-**dibenzyl-α,γ-diphenyldihydropyrazine,** melting at 163°, *N*-**benzyl-α,δ-diphenyl-dihydropyrazine,** etc., are produced by the condensation of amines and phenacyl bromide (B. **27,** R. 134).

αγ-Dihydro-pyrazines are the primary condensation products of the α-amino-aldehydes and α-amino-ketones. On heating with mineral acids they are split up to form the original bodies. Oxidation, even in air only, converts them into the corresponding pyrazines (B. **41,** 1128).

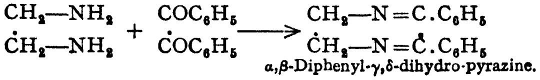
α,γ-Diphenyl-β,δ-dihydropyrazine, $C_6H_5.C\begin{smallmatrix}\diagup N—CH_2 \diagdown\\ \diagdown CH_2—N \diagup\end{smallmatrix}C.C_6H_5$, yellow flakes, m.p. 116°, from ω-aminoacetophenone. **αγ-Diphenyl-βδ-dimethyl-βδ-dihydropyrazine** (2), from α-amino-propriophenone (1), is split up by hydrolysis with HCl principally into the hydrochloride of α-amino-α-phenylacetone (3), which, precipitated from its salt by alkalies, condenses into **α,γ-diphenyl-β,δ-dimethyl-α,γ-dihydropyrazine** (4):



$$\begin{array}{lclclcl}(1) & & (2) & & (3) & & (4)\\ C_6H_5.CO & & C_6H_5.C:N.CH.CH_3 & & C_6H_5.CH.NH_2 & & C_6H_5.CH.N:C.CH_3\\ \vert & \longrightarrow & \vert \qquad\quad \vert & \longrightarrow & \vert & \longrightarrow & \vert \qquad\quad \vert\\ CH_3.CH.NH_2 & & CH_3.CH.N:C.C_6H_5 & & CH_3CO & & CH_3.C:N.CH.C_6H_5\end{array}$$

On oxidation, both isomeric dihydro-pyrazines form the same diphenyl-dimethyl-pyrazine (see above).

αβ-Dihydro-pyrazines are formed from 1,2-diketones with ethylene diamine (B. **22,** 346; **26,** R. 1009):



$$\begin{array}{l}CH_2—NH_2\\ \vert\\ CH_2—NH_2\end{array} + \begin{array}{l}COC_6H_5\\ \vert\\ COC_6H_5\end{array} \longrightarrow \begin{array}{l}CH_2—N=C.C_6H_5\\ \vert \qquad\qquad \vert\\ CH_2—N=C.C_6H_5\end{array}$$

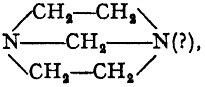
α,β-Diphenyl-γ,δ-dihydro-pyrazine.

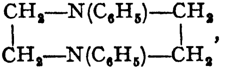
N,N,**α-Triphenyl-tetrahydro-pyrazine,** $\begin{smallmatrix}CH_2—N(C_6H_5)—CH\\ CH_2—N(C_6H_5)—CC_6H_5\end{smallmatrix}$, m.p., 131°, is formed similarly from ethylene diphenyl diamine with phenacyl bromide (B. **26,** R. 93), and the isomeric *N*αβ-**triphenyl tetrahydropyrazine** from ethylene-phenyl-diamine and benzoïn (B. **31,** 1582); compare also the condensation of ethylene-diamine with ketipinic acid ester (C. 1900, II. 175).

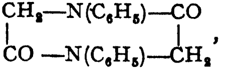
α,γ-Diphenyl-β-keto-β,*N*-dihydro-pyrazine, $C_6H_5.C\begin{smallmatrix}\diagup NH—CO \diagdown\\ \diagdown CH—N \diagup\end{smallmatrix}C.C_6H_5$, m.p. 197°, is formed by the action of gaseous HCl upon an etheric solution of benzaldehyde cyanohydrin. Distillation with zinc-dust converts it into αγ-diphenylpyrazine, and heating with HI and phosphorus into **αγ-diphenyl-β,*N*-dihydropyrazine,** $C_6H_5C\begin{smallmatrix}\diagup NH—CH_2 \diagdown\\ \diagdown CH—N \diagup\end{smallmatrix}C.C_6H_5$, m.p. 164° (C. 1905, II. 236; 1909, I. 1990).

Hexahydro-pyrazines, piperazines, have already been discussed (in Vol. I.) as cyclic dialkylene-imides. In addition to the synthetic methods given there, the piperazines are also prepared by the reduction of the pyrazines with sodium and alcohol (B. **26,** 724).

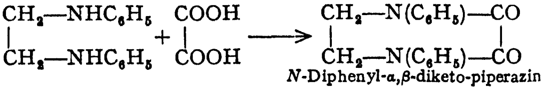
C-**Methylpiperazine,** $C_4H_9(CH_3)N_2$, boils at 155°. *α,γ*-**Dimethylpiperazine** is also formed from lactimide (dimethyl diacipiperazine) by reduction with Na and alcohol (C. 1902, I. 631).

Di- and poly-alkylic piperazines occur each in two stereoisomeric forms: **Di-, Tri-, Tetramethyl-piperazine** (see J. pr. Ch. [2], **55,** 49). *N*-**Dinitropiperazine,** $NO_2.N[CH_2.CH_2]_2N.NO_2$, m.p. 215°, is formed from *N*-diphenyl sulphone piperazine with fuming nitric acid (C. 1909, I. 1579). Consult B. **29,** R. 384, for **methylene piperazine,**  made from piperazine and formaldehyde.

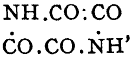
N - **Diphenylpiperazine,** 
$\begin{array}{l}CH_2—N(C_6H_5)—CH_2\\ |\qquad\qquad\qquad\quad |\\ CH_2—N(C_6H_5)—CH_2\end{array}$, melting at 163°, results from the interaction of ethylene bromide and aniline (B. **22,** 1777). *N*-**Dibenzylpiperazine,** melting at 92°, is also produced when caustic potash acts upon bromethylbenzylamine.

The cyclic amino acid anhydrides are *α,γ-diketo-piperazines.* They have already received consideration (Vol. I.) after the *α*-amino-carboxylic acids. **Diphenyldiketopiperazine,** *diphenyldiacipiperazine,* 
$\begin{array}{l}CH_2—N(C_6H_5)—CO\\ |\qquad\qquad\qquad\quad |\\ CO—N(C_6H_5)—CH_2\end{array}$, is formed from anilinoacetic acid. Consult B. **25,** 2919, 3275, etc., for stereoisomeric diacipiperazines.

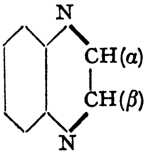
α,β-Diketo-piperazines are produced in the condensation of oxalic acid with derivatives of ethylene diamine (B. **23,** 2028):


$$\begin{array}{l}CH_2—NHC_6H_5\\ |\\ CH_2—NHC_6H_5\end{array} + \begin{array}{l}COOH\\ |\\ COOH\end{array} \longrightarrow \begin{array}{l}CH_2—N(C_6H_5)—CO\\ |\qquad\qquad\qquad\quad |\\ CH_2—N(C_6H_5)—CO\end{array}$$

N-Diphenyl-α,β-diketo-piperazine.

Chromic acid oxidizes this diketopiperazine to a tetraketopiperazine. The simplest **tetraketopiperazine,** 
$\begin{array}{l}NH.CO:CO\\ \dot{C}O.CO.\dot{N}H\end{array}$, has been obtained by the action of sodium alcoholate upon oxaminic acid ester (C. 1909, I. 1892).

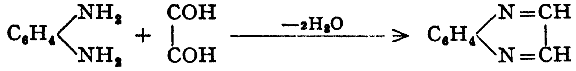
II. BENZOPARADIAZINES.



Quinoxaline.

Quinoxalines.—The quinoxalines, just like the benziminazoles, are condensation products of *o*-diamines. They result:

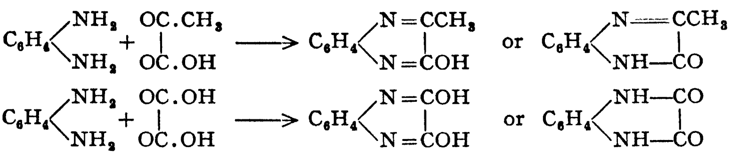
1. By the condensation of *o*-phenylene-diamines with glyoxal and 1,2-diketone compounds (Hinsberg, A. **237,** 327):



$$C_6H_4\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix} + \begin{matrix}COH\\ |\\ COH\end{matrix} \xrightarrow{-2H_2O} C_6H_4\begin{matrix}\diagup N=CH\\ \quad |\\ \diagdown N=CH\end{matrix}$$

Similarly, benzil yields α,β-diphenyl-quinoxaline; dioxy-tartaric acid, α,β-quinoxaline dicarboxylic acid, etc. The reactions are very complete, even at low temperatures.

α-Ketone carboxylic acids—*e.g.*, pyroracemic acid and mesoxalic acid—become *oxyquinoxalines*, while oxalic acid yields *dioxy-quinoxalines* (B. **30,** 768):

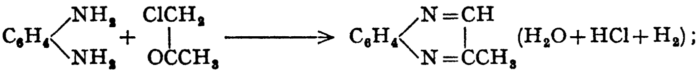


$$C_6H_4\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix} + \begin{matrix}OC.CH_3\\ |\\ OC.OH\end{matrix} \longrightarrow C_6H_4\begin{matrix}\diagup N=CCH_3\\ \quad |\\ \diagdown N=COH\end{matrix} \text{ or } C_6H_4\begin{matrix}\diagup N=\!=CCH_3\\ \quad |\\ \diagdown NH—CO\end{matrix}$$

$$C_6H_4\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix} + \begin{matrix}OC.OH\\ |\\ OC.OH\end{matrix} \longrightarrow C_6H_4\begin{matrix}\diagup N=COH\\ \quad |\\ \diagdown N=COH\end{matrix} \text{ or } C_6H_4\begin{matrix}\diagup NH—CO\\ \quad |\\ \diagdown NH—CO\end{matrix}$$

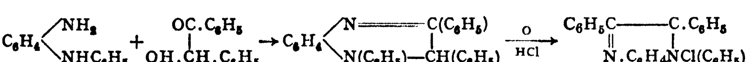
The *o*-naphthylene-diamines react like the *o*-phenylene-diamines, forming *naphtho-quinoxalines*. The tetra-amino-benzenes yield *benzo-diparadiazines*.

2. α-Chloro-keto-compounds, α-aldehyde alcohols, and α-ketone alcohols—*e.g.*, benzoïn, furoïn, arabinose, and glucose—condense with *o*-phenylene-diamines. Water and hydrogen are eliminated and quinoxalines remain:



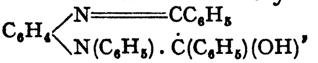
$$C_6H_4\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix} + \begin{matrix}ClCH_2\\ |\\ OCCH_3\end{matrix} \longrightarrow C_6H_4\begin{matrix}\diagup N=CH\\ \quad |\\ \diagdown N=CCH_3\end{matrix}\ (H_2O+HCl+H_2);$$

with mono-alkylic *o*-phenylene-diamines, on the other hand, the products are dihydro-quinoxalines, which ferric chloride oxidizes to azonium salts of the quinoxalines (B. **24,** 719, 1875; **25,** 1627):

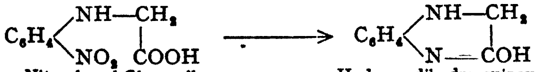


$$C_6H_4\begin{matrix}\diagup NH_2\\ \diagdown NHC_6H_5\end{matrix} + \begin{matrix}OC.C_6H_5\\ |\\ OH.CH.C_6H_5\end{matrix} \rightarrow C_6H_4\begin{matrix}\diagup N=\!=\!=C(C_6H_5)\\ \quad |\\ \diagdown N(C_6H_5)—CH(C_6H_5)\end{matrix} \xrightarrow[HCl]{O} \begin{matrix}C_6H_5C—\!—C.C_6H_5\\ \|\quad\quad |\\ N.C_6H_4NCl(C_6H_5)\end{matrix}$$

o-Amino-diphenyl-amine. Benzoïn. *N*-α,β-Triphenyl dihydro-quinoxaline. Triphenyl-quinoxalinium Chloride.

The azonium salts are immediately produced by the action of mono-alkylic or phenylated *o*-diamines upon 1,2-diketones (B. **25,** 1010; **27,** 2355; **31,** 2425; **32,** 1042). The bases corresponding to these salts are very unstable, as they change to pseudo-bases,  $C_6H_4\begin{matrix}\diagup N=\!=\!=CC_6H_5\\ \diagdown N(C_6H_5).\dot{C}(C_6H_5)(OH)\end{matrix}$, from which the azonium salts are regenerated by acids (see the analogous behaviour of the alkyl-quinolinium hydroxides).

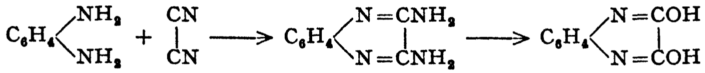
3. *o*-Nitrophenyl α-amino-fatty acids, when reduced, yield *hydroxy-dihydro-quinoxalines*, which are also obtained from *o*-phenylene-diamines and α-haloid fatty acids (A. **292,** 250):



$$C_6H_4\begin{matrix}\diagup NH—CH_2\\ \quad\quad |\\ \diagdown NO_2\ COOH\end{matrix} \longrightarrow C_6H_4\begin{matrix}\diagup NH—CH_2\\ \quad |\\ \diagdown N=\!=COH\end{matrix}$$

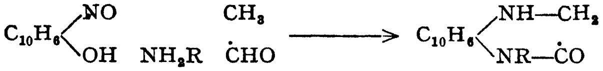
α-Nitrophenyl Glycocoll. α-Hydroxy-dihydro-quinoxaline.

4. *o*-Phenylene-diamines condense with cyanogen to *diamino-quinoxalines,* which dilute hydrochloric acid changes to dihydroxy-quinoxalines:



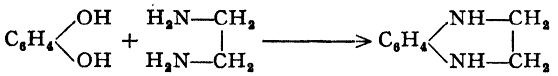
$$C_6H_4\left\langle\begin{array}{l}NH_2\\ NH_2\end{array}\right. + \begin{array}{c}CN\\ |\\ CN\end{array} \longrightarrow C_6H_4\left\langle\begin{array}{l}N=CNH_2\\ \quad\;\;|\\ N=CNH_2\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}N=COH\\ \quad\;\;|\\ N=COH\end{array}\right.$$

5. The condensation of *o*-nitroso-phenols with acetaldehyde and ammonia or primary amines produces hydroxy-dihydro-quinoxalines and keto-tetrahydro-quinoxalines respectively (B. **42,** 574; C. 1908, I. 1589; 1911, I. 178):



$$C_{10}H_6\left\langle\begin{array}{l}NO\\ OH\end{array}\right. \quad NH_2R \quad \begin{array}{c}CH_3\\ \cdot\\ CHO\end{array} \longrightarrow C_{10}H_6\left\langle\begin{array}{l}NH-CH_2\\ \qquad\;\;\cdot\\ NR-CO\end{array}\right.$$

6. *Tetrahydro-quinoxalines* are produced in the condensation of dihydric phenols with alkylenediamines:



$$C_6H_4\left\langle\begin{array}{l}OH\\ OH\end{array}\right. + \begin{array}{l}H_2N-CH_2\\ \qquad\;\;|\\ H_2N-CH_2\end{array} \longrightarrow C_6H_4\left\langle\begin{array}{l}NH-CH_2\\ \qquad\;\;|\\ NH-CH_2\end{array}\right.$$

Behaviour.—The quinoxalines are feeble monacid bases. Their odour resembles that of quinoline or piperidine. They are readily soluble in alcohol and ether, and more sparingly soluble in hot than in cold water. They are stable in the presence of oxidizing agents, while reducing agents convert them into hydroquinoxalines.

Quinoxaline, $C_8H_6N_2$, is obtained from *o*-phenylene-diamine and glyoxal bisulphite. It melts at 27° and boils at 229°. Its **iodo-methylate** melts with decomposition at 175°.

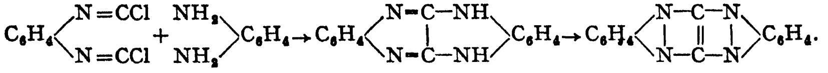
Toluquinoxaline, $CH_3C_6H_3[N_2C_2H_2]$, b.p. 245°, from toluylene-*o*-diamine. **αβ-Dimethylquinoxaline,** $C_6H_4[N_2C_2(CH_3)_2]$, m.p. 106°, and **α,β-Dimethyl-toluquinoxaline,** $CH_3C_6H_3[N_2C_2(CH_3)_2]$, m.p. 54°, b.p. 270°, from phenylene and toluylene diamine respectively with diacetyl. **α-*iso*Propyl-quinoxaline,** b.p. 270°, by condensation of *o*-phenylene diamine with γ-bromo-αα-dimethyl aceto-acetic ester and subsequent heating with HCl (B. **32,** 1209). **Phenylquinoxaline,** $C_8H_5N_2(C_6H_5)$, m.p. 78°, by the condensation of *o*-phenylene-diamine with *iso*nitroso-acetophenone and by disintegration of αβ-naphtho-phenazine (B. **39,** 2238). Similarly, α- and **β-phenyl-naphtho-quinoxaline,** m.p. 153° and 163° respectively, have been obtained from *iso*nitrosoacetophenone and αβ-naphthylene diamine, as well as the decomposition of the two αβ-naphthazines (B. **41,** 2350).

α,β-Diphenylquinoxaline, $C_8H_4N_2(C_6H_5)_2$, melts at 124° (B. **27,** 2181).

***Bz*-Chloroxy-α,β-diphenylquinoxaline** has been recommended as an indicator in alkalimetry under the name of *luteol* (B. **28,** R. 628).

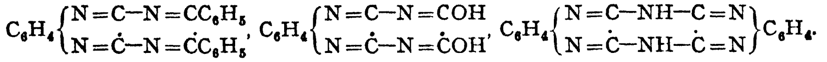
Oxyquinoxaline, $C_8H_4[N_2C_2H(OH)]$, melting at 265°, is made from its carboxylic acid (see below).

α-Methyl-β-oxytoluquinoxaline, $CH_3C_6H_3[N_2C_2(CH_3)(OH)]$, melting at 220°, and **α-Phenyl-β-oxy-toluquinoxaline,** $CH_3C_6H_3[N_2C_2(C_6H_5)(OH)]$, melting at 196°, are prepared from toluylenediamine with pyroracemic acid and phenylglyoxylic acid. They are soluble both in alkalies and in acids. The solutions of the first are colourless, and those of the second yellow in colour. **α,β-Dioxyquinoxaline,** $C_6H_4[N_2C_2H_2O_2]$, from *o*-phenylenediamine and oxalic acid, or α,β-diaminoquinoxaline (see above) by means of hydrochloric acid is converted by PCl_5 into **α,β-dichloroquinoxaline,** melting at 150°. When the latter is digested with *o*-phenylenediamine a condensation results, the solutions of which are yellow in colour and exhibit an intense yellow-green fluorescence. This fact has given it the name **fluoflavine,** $C_6H_4:(N_4C_2H_2):C_6H_4$, melting at 360°. It loses two hydrogen atoms when it is oxidized, and becomes **quinoxalophenazine,** $C_6H_4:(N_4C_2):C_6H_4$ (B. **29,** 784):



$$C_6H_4\left\langle\begin{matrix}N=CCl\\N=CCl\end{matrix}\right. + \left.\begin{matrix}NH_2\\NH_2\end{matrix}\right\rangle C_6H_4 \rightarrow C_6H_4\left\langle\begin{matrix}N-C-NH\\ \vert\\ N-C-NH\end{matrix}\right\rangle C_6H_4 \rightarrow C_6H_4\left\langle\begin{matrix}N-C-N\\ \vert\quad\Vert\quad\vert\\ N-C-N\end{matrix}\right\rangle C_6H_4.$$

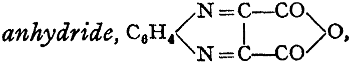
αβ-Diaminoquinoxaline, from *o*-phenylene-diamine and cyanogen gas in methyl alcoholic solution, condenses with *o*-diketones like benzil and phenanthrene-quinone, with pyro-racemic acid, and with oxalic acid, thus resembling the *o*-phenylene-diamines, all forming *polycyclic nuclei;* with αβ-dichloro-quinoxaline it forms the so-called *fluorubine*:



$$C_6H_4\begin{Bmatrix}N=C-N=CC_6H_5\\N=\dot{C}-N=\dot{C}C_6H_5\end{Bmatrix}, \quad C_6H_4\begin{Bmatrix}N=C-N=COH\\N=\dot{C}-N=\dot{C}OH\end{Bmatrix}, \quad C_6H_4\begin{Bmatrix}N=C-NH-C=N\\N=\dot{C}-NH-\dot{C}=N\end{Bmatrix}C_6H_4.$$

α,β-Dioxy-naphtho-quinoxaline, *Naphthylene Oxamide,* $C_{10}H_6$-$(N_2C_2O_2H_2)$ (B. **30,** 772).

α,β-**Quinoxalinedicarboxylic Acid,** $C_6H_4[N_2C_2(COOH)_2](+2H_2O)$, from dioxytartaric acid and *o*-phenylenediamine, melts at 190° with decomposition (B. **27,** 2185). It forms an *anhydride,*

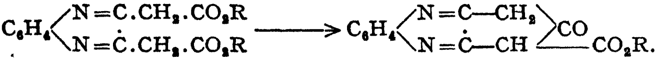


$$C_6H_4\left\langle\begin{matrix}N=C-CO\\ \vert\\ N=C-CO\end{matrix}\right\rangle O,$$

melting at 251°. Ammonia converts the latter into quinoxaline dicarbonamic acid, which with bromine and caustic potash yields **α-aminoquinoxaline-β-carboxylic acid,** $C_6H_4[N_2C_2(NH_2)(COOH)]$, melting with decomposition at 210° (B. **28,** 1657).

α-Oxyquinoxaline-β-carboxylic Acid, $C_6H_4[N_2C_2(OH)(COOH)]$ melting at 265° with decomposition, is produced by saponifying the acid ureïde produced in the interaction of alloxan and *o*-phenylenediamine (A. **292,** 248).

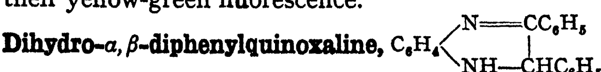
αβ-Quinoxaline diacetic ester, $C_8H_4N_2(CH_2CO_2C_2H_5)_2$, m.p. 58°, from *o*-phenylenediamine and ketipinic acid ester, is condensed by Na ethylate to pheno*cyclo*pentanoneazine carboxylic ester (C. 1901, II. 539):



$$C_6H_4\left\langle\begin{matrix}N=C.CH_2.CO_2R\\N=\dot{C}.CH_2.CO_2R\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}N=C-CH_2\\N=\dot{C}-CH\end{matrix}\right\rangle CO \atop \quad CO_2R.$$

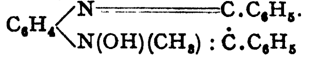
Hydroquinoxalines.—The *N*,α-dihydroquinoxalines are distinguished by their yellow-green fluorescence.

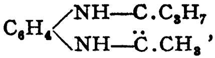
Dihydro-α,β-diphenylquinoxaline,

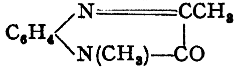


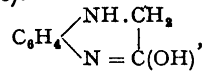
$$C_6H_4\left\langle\begin{matrix}N=\!=CC_6H_5\\ \vert\\ NH-CHC_6H_5\end{matrix}\right.,$$

melts at 146°, and is produced in the reduction of diphenylquinoxaline with stannous chloride, or from benzoïn and *o*-phenylenediamine (B. **24,** 1870; **27,** 2182). ***N*-Methyldihydro-α,β-diphenylquinoxaline** (B. **25,** 1632) is oxidized to N-*Methyl-α,β-diphenyl-quinoxalinium-hydroxide,*


$C_6H_4\left\langle\begin{array}{l}N=\!=\!=\!=\!=C.C_6H_5.\\ N(OH)(CH_3):\dot{C}.C_6H_5\end{array}\right.$

***N,N*₁-Dihydro-α-methyl-β-*iso*propylquinoxaline,**  $C_6H_4\left\langle\begin{array}{l}NH-C.C_3H_7\\ NH-\dot{C}.CH_3\end{array}\right.$, colourless flakes, m.p. 124°, by condensation of *o*-phenylenediamine with mesityl oxide. Its dinitroso-compound melts at 177° (B. **39,** 1646).

***N*-Methylketodihydro-β-methylquinoxaline,** *N,β-Dimethylquinoxalone,*  $C_6H_4\left\langle\begin{array}{l}N=\!=\!=\!=CCH_3\\ \qquad\qquad\;|\\ N(CH_3)-CO\end{array}\right.$, melts at 78° and boils at 308°. It results from the condensation of methyl-*o*-phenylene-diamines and pyroracemic acid (B. **25,** 1630).

Oxydihydroquinoxaline,  $C_6H_4\left\langle\begin{array}{l}NH.CH_2\\ \quad\;\;|\\ N=C(OH)\end{array}\right.$, m.p. 132°, from *o*-phenylenediamine with monochloracetic acid, is oxidized by chromic acid to dioxyquinoxaline (B. **41,** 800).

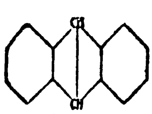
Oxy-dihydronaphthoquinoxaline, m.p. 246°, from α-nitroso-β-naphthol, acetaldehyde, and ammonia.

Tetrahydroquinoxaline, $C_8H_{10}N_2$, melting at 97° and boiling at 289°, is obtained from pyrocatechol and ethylenediamine (B. **21,** 378), or by saponifying its *dibenzosulphonic derivative,* $C_6H_4(NSO_2C_6H_5)_2>(CH_2)_2$, the reaction-product of ethylene bromide and dibenzene sulphon-*o*-phenylenediamine (B. **28,** R. 756).

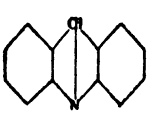
α,β-**Diphenyltetrahydroquinoxaline,** $C_8H_8N_2(C_6H_5)_2$, is produced in two isomeric forms, melting at 105° and 142°, when diphenylquinoxaline is reduced with sodium and alcohol (B. **27,** 2184).

III. DIBENZOPARADIAZINES.

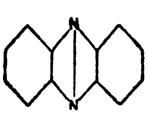
Phenazine Group.—Phenazine is analogous in constitution to anthracene and acridine:



Anthracene.

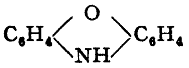


Acridine.

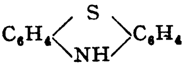


Phenazine.

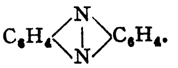
On the other hand, it is, in its methods of formation and general deportment, very closely related to the dibenzo-derivatives of paroxazine and parathiazine:


$C_6H_4\left\langle\begin{array}{c}O\\ NH\end{array}\right\rangle C_6H_4$

Dibenzoparoxazine,
Phenoxazine.


$C_6H_4\left\langle\begin{array}{c}S\\ NH\end{array}\right\rangle C_6H_4$

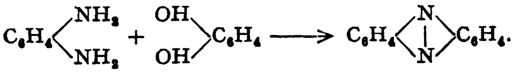
Dibenzoparathiazine,
Thiodiphenylamine.


$C_6H_4\left\langle\begin{array}{c}N\\ |\\ N\end{array}\right\rangle C_6H_4.$

Dibenzoparadiazine,
Phenazine.

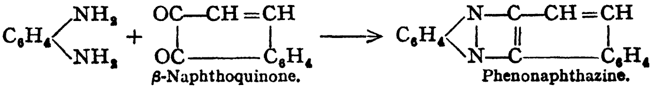
It is the parent substance of an extensive class of dyestuffs, which are to some degree quite important from the technical standpoint—*e.g.*, the eurhodines, toluylene-red, the indulines, safranines, etc.—which are in part derived from phenazine itself and partly from higher condensed paradiazines—*e.g.*, naphthophenazine, naphthazine, etc.

Methods of Formation.—1. Phenazines result by the exit of water and hydrogen in the condensation of *o*-diamines and *o*-dihydroxybenzenes:



$$C_6H_4\begin{matrix}NH_2\\NH_2\end{matrix} + \begin{matrix}OH\\OH\end{matrix}C_6H_4 \longrightarrow C_6H_4\begin{matrix}N\\|\\N\end{matrix}C_6H_4.$$

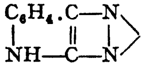
2. Azines are also produced from *o*-diamines and *o*-quinones—*e.g.*, β-naphthoquinone, phenanthraquinone, croconic acid, etc.:



$$C_6H_4\begin{matrix}NH_2\\NH_2\end{matrix} + \begin{matrix}OC—CH=CH\\|\qquad\quad|\\OC———C_6H_4\end{matrix} \longrightarrow C_6H_4\begin{matrix}N—C—CH=CH\\|\quad\|\qquad\quad|\\N—C———C_6H_4\end{matrix}$$

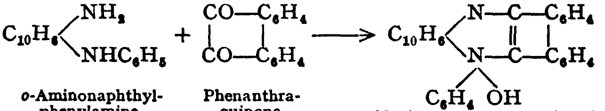
β-Naphthoquinone. Phenonaphthazine.

Isatin and *o*-phenylenediamine similarly yield ***indophenazine***,



$$\begin{matrix}C_6H_4.C—N\\|\quad\ \|\quad|\\NH—C—N\end{matrix}C_6H_4$$

(B. **29**, 200). On the other hand, ***azonium bases*** result if mono-substituted *o*-diamines and *o*-quinones are condensed (see quinoxaline):

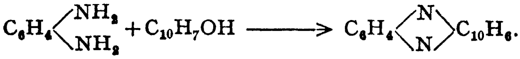


$$C_{10}H_6\begin{matrix}NH_2\\NHC_6H_5\end{matrix} + \begin{matrix}CO—C_6H_4\\|\qquad|\\CO—C_6H_4\end{matrix} \longrightarrow C_{10}H_6\begin{matrix}N—C—C_6H_4\\|\quad\|\quad|\\N—C—C_6H_4\\C_6H_4\ \ OH\end{matrix}$$

o-Aminonaphthyl-phenylamine. Phenanthraquinone. Naphtho-phenanthra-phenyl-azonium Hydroxide.

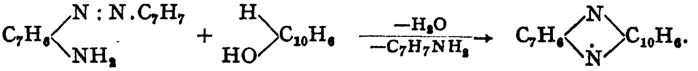
Such ***azonium*** compounds are also produced by the action of azines and alkyl iodides, and by the deamination of induline and safranine bases.

3. Furthermore, azines result in the oxidation of a mixture of *o*-diamines and α-naphthol:



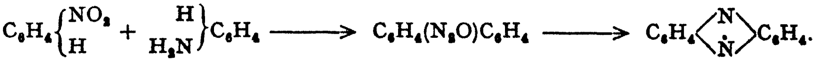
$$C_6H_4\begin{matrix}NH_2\\NH_2\end{matrix} + C_{10}H_7OH \longrightarrow C_6H_4\begin{matrix}N\\N\end{matrix}C_{10}H_6.$$

4. Naphtho-phenazines and naphthazines are formed by the fusion of *o*-amino-azo-compounds with β-naphthol (B. **38**, 1811):



$$C_7H_6\begin{matrix}N:N.C_7H_7\\NH_2\end{matrix} + \begin{matrix}H\\HO\end{matrix}C_{10}H_6 \xrightarrow[-C_7H_7NH_2]{-H_2O} C_7H_6\begin{matrix}N\\ \cdot\\N\end{matrix}C_{10}H_6.$$

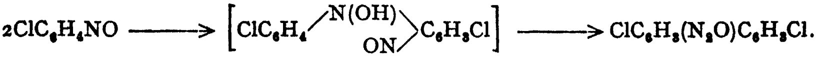
5. Nitrobenzenes and anilines or naphthylamines, treated with dry KHO, form phenazines and phenazine oxides respectively, the latter being easily reduced to phenazines (B. **34**, 2442):



$$C_6H_4\begin{cases}NO_2\\H\end{cases} + \left.\begin{matrix}H\\H_2N\end{matrix}\right\}C_6H_4 \longrightarrow C_6H_4(N_2O)C_6H_4 \longrightarrow C_6H_4\begin{matrix}N\\ \cdot\\N\end{matrix}C_6H_4.$$

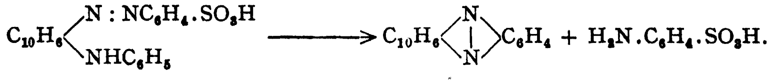
6. Phenazine oxides are also formed by the action of concentrated SO_4H_2 upon para-substituted nitrosobenzenes (when the

p-position is unoccupied, *p*-nitrosodiphenyl hydroxylamines are formed) (A. **382,** 82):



$$2ClC_6H_4NO \longrightarrow \left[ClC_6H_4\langle{}^{N(OH)}_{ON}\rangle C_6H_3Cl\right] \longrightarrow ClC_6H_3(N_2O)C_6H_3Cl.$$

7. By the decomposition of *o*-anilino-(toluino-, etc.)-azo-bodies. Thus, *o*-anilino-naphthyl-azobenzene-sulphonic acid, produced by the combination of phenylnaphthylamine with diazobenzene-sulphonic acid, breaks down, on boiling with dilute acids, into naphthophenazine and sulphanilic acid:



$$C_{10}H_6\langle{}^{N:NC_6H_4.SO_3H}_{NHC_6H_5} \longrightarrow C_{10}H_6\langle{}^{N}_{N}\rangle C_6H_4 + H_2N.C_6H_4.SO_3H.$$

Behaviour.—The phenazines are mostly yellow-coloured, feebly basic bodies that cannot be distilled without suffering decomposition. They dissolve in concentrated sulphuric acid with a red to blue colour. They are again precipitated upon addition of water. They combine with alkyl iodides to azonium iodides. They are reduced to colourless dihydro-compounds—*e.g.*, *dihydrophenazine*, $C_6H_4<{}^{NH}_{NH}>C_6H_4$—which are readily re-oxidized to azines.

Phenazine, $C_{12}H_8N_2$, was first obtained from calcium azobenzoate by distillation, and was called *azodiphenylene*, with which it is isomeric. It may also be prepared from *o*-phenylene-diamine and pyrocatechol, and by conducting aniline vapours through a tube heated to redness, by the deamination of aminophenazines, and upon boiling formazyl carboxylic ester, $CO_2R.C\langle{}^{N.NHC_6H_5}_{N:NC_6H_5}$, with concentrated acids (B. **25,** 3205), together with various other products in the oxidation of *o*-amino-diphenylamine, $C_6H_4<{}^{NH.C_6H_5}_{NH_2}$ (B. **26,** 383). It melts at 171°.

Phenazine is also obtained from nitrobenzene, aniline, and caustic potash. In this process some phenazine oxide, $C_6H_4(N_2O)C_6H_4$, m.p. 226°, is obtained, which is reduced quantitatively to phenazine by stannous chloride (B. **34,** 2446).

Ammonium sulphide reduces phenazine to *dihydrophenazine*. Consult A. **292,** 260, for its reduction in acid solutions.

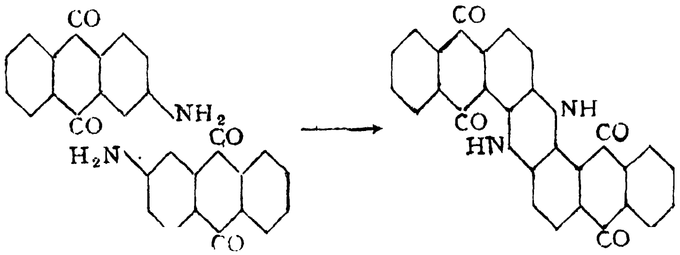
Dimethylphenazine, $CH_3.C_6H_3:N_2:C_6H_3.CH_3$, m.p. 162°, by reducing **dimethylphenazine oxide,** m.p. 205°, obtained from *p*-nitrosotoluene by method 6 (see above).

Toluphenazine, $CH_3.C_6H_3:N_2:C_6H_4$, melting at 117°, is obtained from toluylene-diamine and pyrocatechol; also from *o*-amino-phenyl-tolylamine and lead oxide (B. **29,** 1873).

α,β-**Naphthophenazine,** $C_{10}H_6:N_2:C_6H_4$, melting at 142°, is produced, in addition to the common methods (see above), from naphthyl-phenyl-nitrosamine, $C_{10}H_7\backslash\overset{NO}{\underset{N}{|}}/C_6H_5$, just as acridin is obtained from formyldiphenylamine. *Sym. α,β*-**naphthazine,** $C_{10}H_6:N_2:C_{10}H_6$, melting at 243°, is formed in like manner from *β,β*-dinaphthyl-nitrosamine (B. **26**, 185), or from benzeneazo-β-naphthylamine by fusion with β-naphthol (B. **38**, 1816). *Unsym.-a,β-***Naphthazine,** melting at 283°, was first made by heating nitronaphthalene with lime (*naphthase,* Laurent, 1840), and was consequently long regarded as azonaphthalene. It was also prepared from a,β-naphthylenediamine and β-naphthoquinone. It is most easily made by condensing nitroso-β-naphthylamine and a-naphthylamine (B. **29**, 2086), or by fusing β-naphthylamine with caustic alkalies with or without oxidizers (C. 1905, II. 1757). Oxidative disintegration converts *sym.-aβ*-naphthazine into a-phenyl-naphtho-quinoxaline, and *unsym.-aβ*-naphthazine into β-phenyl-naphtho-quinoxaline (B. **41**, 390).

Phenanthrophenazine, $C_{14}H_8:N_2:C_6H_4$, melts at 234°, and is obtained from acenaphthene-quinone and o-phenylenediamine (C. 1899, II. 338).

Anthrazine, $C_{14}H_8\left\{\begin{matrix}[1]N[1]\\ [2]\dot{N}[2]\end{matrix}\right\}C_{14}H_8$, reddish-brown needles, m.p. about 390°, subliming, results from fusing β-anthramine with caustic alkalies (C. 1906, II. 725). It is also obtained from **Indanthrene,** *Dihydroanthraquinoneazine,* by distillation with zinc-dust. Indanthrene is formed from 2-amino-anthraquinone by fusion with KHO at 250°:



2-Amino-anthraquinone. Indanthrene.

The following methods of formation, which have no technical importance, prove its constitution: (1) By condensation of 1,2-diamino-anthraquinone with 1,2-anthraquinone, followed by oxidation and reduction (C. 1906, II. 80); (2) from 1-amino-anthraquinone on heating with dilute acids under pressure (C. 1907, II. 1133); (3) by auto-condensation of 1-amino-2-bromo(chloro)anthraquinone (C. 1905, I. 843). Indanthrene is a blue powder very slightly soluble in organic solvents. From quinoline it crystallizes in needles with a coppery lustre. On heating with benzoyl-chloride it yields a dibenzoyl compound in red needles (B. **44**, 1732).

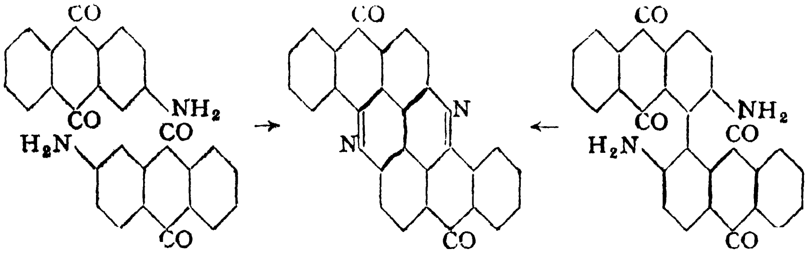
By oxidation with chromic or nitric acid, indanthrene passes into the greenish-yellow **anthraquinonazine,** $C_{14}H_6O_2(N_2)C_{14}H_6O_2$, which easily regenerates the dihydroazine. The stability of dihydroanthraquinonazine, remarkable when compared with the instability of other dihydrophenazines, is paralleled by the stability of fluorubin, etc. On strong oxidation with chromic acid indanthrene passes into **dioxy-pyrazino-anthraquinone,** Hydrosulphite or zinc-dust reduces indanthrene, with absorption of 2 or 4 atoms of hydrogen to products similar to hydro-quinone soluble in alkalies. These, by oxidation in air, regenerate the insoluble dye-stuff. This is the basis of vat-dying with indanthrene (B. **36,** 3410; **40,** 390).

Technical importance attaches to a series of halogen substitution products of indanthrene which are oxidized to the corresponding azines with even greater difficulty than indanthrene itself (compare B. **43,** 1000).

Closely related to indanthrene in its behaviour and its methods of formation is the yellow dye—

Flavanthrene (for constitution, see below), which, though it does not belong to the *p*-diazines, will be dealt with here on account of its close relation to indanthrene.

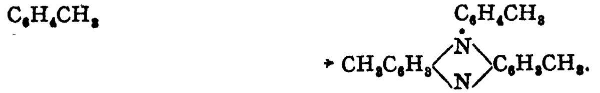
Flavanthrene is also obtained from 2-amino-anthraquinone by potash fusion at high temperatures (350°), or, better, by boiling with antimony pentachloride in nitrobenzene solution. Its constitution follows from its synthesis from 2,2′-dimethyl-1,1′-dianthraquinonyl. By oxidation, this is converted into the corresponding dianthraquinonyl dicarboxylic acid, whose diamide, with bromine and alkali, yields 2,2′-diamino-1,1′-dianthraquinonyl, which splits off $2H_2O$ and condenses spontaneously to flavanthrene (B. **40,** 1691; compare M. **32,** 447):



2-Amino-anthraquinone. Flavanthrene. 2,2′-Diamino-1,1′-dianthraquinonyl.

Flavanthrene is a yellow, almost insoluble powder, crystallizing from quinolin in brownish-yellow lustrous needles. On treatment with alkaline hydrosulphite solution it yields a dark-blue vat dye which colours cotton in blue tints, passing on air oxidation into a very fast yellow. Strong reduction with HI and phosphorus, or heating with zinc-dust, converts flavanthrene into the de-oxygenated **flavanthrine,** $C_{28}H_{16}N_2$, brown needles, m.p. 390°, which corresponds to anthrazine (B. **41,** 2304, 2534).

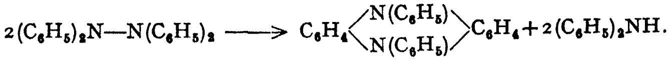
N-Diaryl-dihydro-phenazines are produced by the action of acids upon diaryl-hydroxylamines:



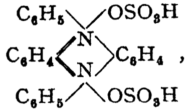
$$C_6H_4CH_3 \qquad \rightarrow CH_3C_6H_3\left\langle\begin{matrix} \overset{C_6H_4CH_3}{N} \\ N \end{matrix}\right\rangle C_6H_3CH_3.$$

The primary formation of diaryl-hydroxylamines is also responsible for the production of diaryl-dihydrophenazines during the action of concentrated acids upon tetra-aryl-hydrazines and tetra-aryl-tetrazones (B. **41**, 3478, 3498; **45**, 496).

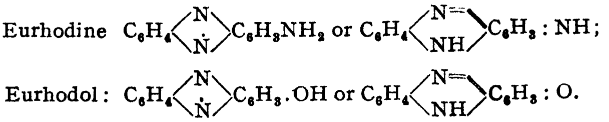
N-**Diphenyl-dihydro-phenazine**, colourless needles, m.p. 172°–175°, is formed besides diphenylamine on boiling tetraphenylhydrazine in toluol solution. Here we must assume a primary decomposition of the tetraphenylhydrazine between the two N-atoms as in the spontaneous dissociation of hexaphenylethane in triphenylmethyl (A. **381**, 202):



$$2(C_6H_5)_2N—N(C_6H_5)_2 \longrightarrow C_6H_4\left<\begin{matrix}N(C_6H_5)\\N(C_6H_5)\end{matrix}\right>C_6H_4+2(C_6H_5)_2NH.$$

The colourless solution of diphenyldihydrophenazine in concentrated H_2SO_4 is coloured an intense blue on adding oxidizing agents, an ortho-quinoid sulphate,  $C_6H_4\left<\begin{matrix}\overset{C_6H_5\diagdown\diagup OSO_3H}{N}\\ \underset{C_6H_5\diagup\diagdown OSO_3H}{N}\end{matrix}\right>C_6H_4$, being formed, which is the carrier for the well-known nitric acid reaction with diphenylamine and sulphuric acid. The tetraphenylhydrazine first obtained in this reaction by the oxidation of diphenylamine is split up by the sulphuric acid into diphenylamine and diphenylhydroxylamine, which immediately condenses to diphenyldihydrophenazine (A. **381**, 210).

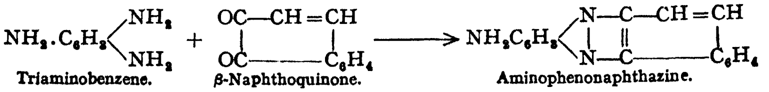
The entrance of salt-forming groups, like NH_2 and OH, converts the phenazines into dyestuffs. In addition to the normal formulas, *paraquinoid* pseudo-forms come into consideration for these amino- and hydroxyphenazines (eurhodines and eurhodols) (A. **290**, 260):



Eurhodine $C_6H_4\left<\begin{matrix}N\\ \dot{N}\end{matrix}\right>C_6H_3NH_2$ or $C_6H_4\left<\begin{matrix}N=\\NH\end{matrix}\right>C_6H_3 : NH$;

Eurhodol: $C_6H_4\left<\begin{matrix}N\\ \dot{N}\end{matrix}\right>C_6H_3.OH$ or $C_6H_4\left<\begin{matrix}N=\\NH\end{matrix}\right>C_6H_3 : O$.

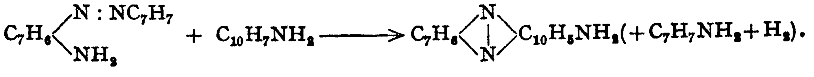
Amino-phenazines.—(*a*) *Monamino-phenazines*, the eurhodines, are produced (1) analogously to the parent substances from aminated *o*-diamines and quinones:



$$NH_2.C_6H_3\left<\begin{matrix}NH_2\\NH_2\end{matrix}\right. + \begin{matrix}OC—CH=CH\\ |\qquad\quad |\\ OC———C_6H_4\end{matrix} \longrightarrow NH_2C_6H_3\left<\begin{matrix}N—C—CH=CH\\ |\quad \|\qquad\quad |\\ N—C———C_6H_4\end{matrix}\right.$$

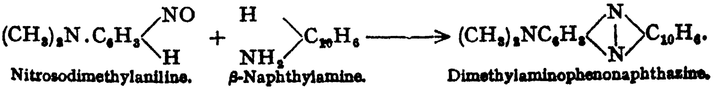
Triaminobenzene. β-Naphthoquinone. Aminophenonaphthazine.

(2) By the action of aromatic monamines upon *o*-aminoazo-bodies:



$$C_7H_6\left<\begin{matrix}N : NC_7H_7\\NH_2\end{matrix}\right. + C_{10}H_7NH_2 \longrightarrow C_7H_6\left<\begin{matrix}N\\ |\\ N\end{matrix}\right>C_{10}H_5NH_2(+C_7H_7NH_2+H_2).$$

(3) By the condensation of quinone dichlorimides or *p*-nitrosodimethyl aniline with monamines, in which the *p*-position is occupied (if this be free, indamines result):



$$(CH_3)_2N.C_6H_3\left<\begin{matrix}NO\\H\end{matrix}\right. + \left.\begin{matrix}H\\NH_2\end{matrix}\right>C_{10}H_6 \longrightarrow (CH_3)_2NC_6H_3\left<\begin{matrix}N\\ |\\ N\end{matrix}\right>C_{10}H_6.$$

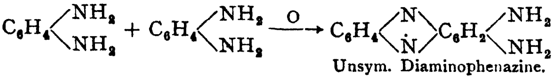
Nitrosodimethylaniline. β-Naphthylamine. Dimethylaminophenonaphthazine.

The eurhodines are feeble bases. Their salts are scarlet red in colour. They dissolve in concentrated sulphuric acid with a carmine-red colour, which, upon the addition of water, passes successively into black, green, and finally red, which is due to the gradual dissociation of polybasic salts, only stable in the presence of concentrated acids. The ethereal solutions have a yellow-green fluorescence. If heated with acids, eurhodines become oxyphenazines. They are not applicable technically.

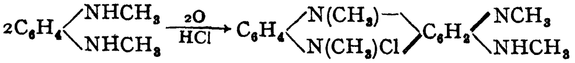
Aminophenazine, $C_6H_4(N_2)C_6H_3NH_2$, has been prepared from *o*-diaminophenazine upon heating it with zinc-dust. It results in the oxidation of the diamino-diphenyl-amines, $NH_2[2]C\ H_4NHC_6H_4[3]NH_2$, or $(NH_2)_2[2,4]C_6H_3NHC_6H_5$ (B. **29,** 1874). It consists of red bronze needles that melt at 265°. It is also prepared by the condensation of *o*-nitroaniline with aniline and zinc chloride (B. **43,** 2186).

Aminonaphthophenazine, $C_{10}H_6N_2C_6H_3NH_3$, m.p. 267°, from chrysoïdin and *β*-naphthol, or from *β*-naphthylamine and quinone dichlorimine (B. **38,** 1844).

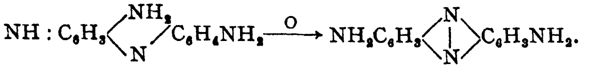
(*b*) *Unsymmetrical diaminophenazines* are formed by the oxidation of *o*-diamines (beside hydroxyaminophenazines, B. **36,** 4026):


Unsym. Diaminophenazine.

On oxidizing dialkylated *o*-diamines, paraquinoid azonium salts are formed (B. **37,** 552):



(*c*) *Symmetrical diaminophenazines, Toluylene-red Group.*—Symmetrical diamino-phenazines are produced when aminated indamines are oxidized (II, 238):


Sym. *o*-Aminophenazine.

Instead of using the prepared indamine, a mixture of a *p*-diamine with a *m*-diamine may be oxidized, or quinone chlorimides may be allowed to act upon a *m*-diamine. Thus, **toluylene-red, dimethyldiaminotoluphenazine,** $NH_2C_7H_5N_2C_6H_3N(CH_3)_2$, is produced by oxidizing dimethylparaphenylenediamine with *m*-toluylenediamine. Toluylene-blue appears as an intermediate product.

It crystallizes in orange-red needles. It is applied in dyeing under the name *Neutral Red*. Its monacid salts are rose-red in colour; the diacid, blue; and the triacid, green; the last two are stable only in the presence of strong acids. It colours silk and cotton, mordanted with tannin, a scarlet-red. It yields *dimethylmonaminotoluphenazine* by deamination.

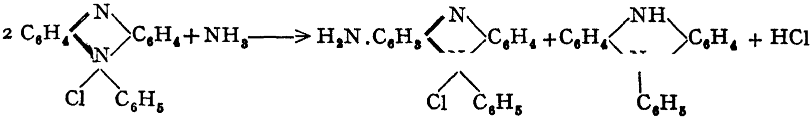
Hydroxyphenazines, *eurhodols,* are formed (1) when the aminophenazines are heated to 180° with concentrated hydrochloric acid; (2) synthetically by condensing *o*-diamines with *o*-quinones containing hydroxyl. The eurhodols resemble the eurhodines in colour and fluorescence.

α-Hydroxynaphthophenazine, $HOC_6H_3N_2C_6H_4$, from aminonaphtho phenazine or produced by the condensation of hydroxy-β-naphthoquinone with *o*-phenylene-diamine, yields two isomeric *methyl ethers*—an oxygen and a nitrogen ether—corresponding to the two formulas presented for eurhodol.

Dihydroxyphenazines are obtained similarly to the monhydroxy bodies. The condensation of *o*-phenylene-diamine with dioxy-diketo-tetrahydro-naphthalene (produced by the action of hypochlorous acid upon β-naphthoquinone) gives rise to **naphthophenazine oxide,** $C_6H_4N_2C_{10}H_6{>}O$. This is a body resembling ethylene oxide. Hydrochloric acid rearranges it into **β-hydroxynaphthophenazine,** $C_6H_4N_2C_{10}H_5OH$, melting at 198° (B. **26,** 617; A. **286,** 61).

Azonium Compounds.—These are important because they are to be regarded as the parent substances of the dyestuffs of the induline, indone, and safranine series, from which they are produced by diazotizing in strongly acid solution, and to which they revert upon treatment with ammonia or alkalies.

When these phenazonium compounds are treated with alkalies, amines, etc., the *p*. position to the N-atom is readily substituted by -OH, NH_2, etc., another molecule of the azonium compound being simultaneously reduced. This is made clearer by an *ortho*-quinonoid formula (see B. **31,** 3073; **33,** 395):



See under diphenyl phenazines for their synthetic methods of formation. The phenylazonium salts have been chiefly isolated by means of their *ferric chloride double salts.* **Ethylphenazonium iodide, Methyl naphthophenazonium iodide,** $C_6H_4(N_2.C_2H_5I)C_6H_4$ and $C_{10}H_6(N_2CH_3I)$-$C_{10}H_6$, are produced by the union of the corresponding azines and alkyl iodides (B. **30,** 391). **Phenylphenazonium chloride** results from the deamination of aposafranine chloride. The *ferric chloride double salt,* $C_6H_4(N_2C_6H_5.Cl)C_6H_4.FeCl_3$, melts at 186°. On reduction with stannous chloride it gives *N*-**Phenyldihydrophenazine,** $C_6H_4{<}\substack{N(C_6H_5)\\ NH}{>}C_6H_4$, m.p. 143°, the true analogue of phenoxazine and thio-diphenylamine (A. **322,** 69). **Phenylnaphthophenazonium chloride,** $C_{10}H_6(N_2C_6H_5.Cl)$-C_6H_4, is obtained from rosinduline and isorosinduline. An isomeric *iso***phenylnaphthophenazonium chloride** has been prepared from ψ-rosinduline (p. 298), and also by condensation of β-naphthoquinone with phenyl-*o*-phenylenediamine (B. **29,** 2316, 2967; **30,** 2629).

Phenyl-dinaphthazonium chloride, $C_{10}H_6(N_2C_6H_5.Cl)C_{10}H_6$, from naphthinduline (B. **32,** 939). **Phenyl-phenanthro-phenazonium chloride,** *Flavinduline,* $C_{14}H_8(N_2C_6H_5Cl)C_6H_4$, from phenanthrene quinone and *o*-amino-diphenylamine (A. **292,** 266; C. 1898, II. 691; 1900, II. 117, etc.).

On the products of the action of magnesium-organic compounds upon flavinduline, see B. **42,** 1104.

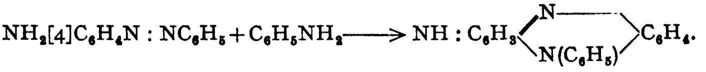
Phenylacenaphthophenazonium nitrate, $C_{12}H_6(N_2C_6H_5NO_3)C_6H_4$, from acenaphthene-quinone and *o*-amino-diphenylamine (B. **43,** 441).

Indulines, Indones, and Safranines.—These dyestuffs bear the same relation to the phenazines as the oxazimes and oxazones (p. 263) to phenoxazine and phenoxazonium salts, and the thiazines and thiazones to thiodiphenylamine and the phenazothionium salts. They contain, instead of the ring-oxygen atom and the ring-sulphur atom of these compounds, an NR-group. The induline salts can be converted, by means of their diazo-bodies, through deamination, into *azonium salts* (p. 296), and must therefore be viewed as aminated azonium salts.

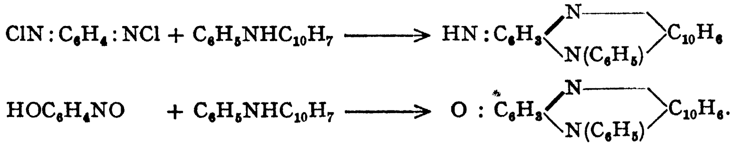
The corresponding azonium hydrates, however, easily split off H_2O and pass into imines which, in contrast with the azonium compounds, are non-electrolytes (B. **29,** 2316, 2752, 2771; **33,** 311). These imines are isomeric or desmotropic with the para-quinone formulæ of the induline bases; according to these formulæ the indulines, indones, etc., are quino-anils, indamines, and indo-phenols, in which the two aromatic nuclei are linked by the NR-group.

To save space, the paraquinonoid formulæ for the bases are mostly employed; they will be readily understood from what has been expressed above. The radical (R) may be an alkyl- or an alkyl-group. The phenylated derivatives primarily are important technically (A. **286,** 187; B. **28,** 1579).

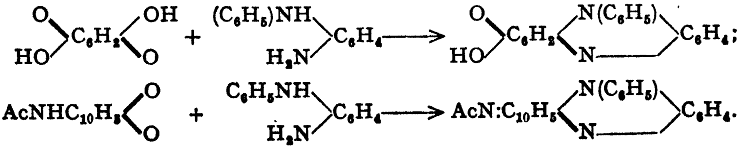
The *indulines* are prepared universally (1) by heating *p*-aminazo-bodies with monamines in the presence of some mineral acid:



The intermediate and by-products in this reaction are *p*-quinone di-imide derivatives—*e.g.*, quinone dianil, anilidoquinone dianil, dianilidoquinone dianil, or azophenine (Vol. II.), etc. They are to be considered as the real generators of the indulines (B. **25,** 2731; C. 1902, II. 902). Hence there is a relation between this reaction and the formation of naphthindulines and -indones (*iso*rosindulines and *iso*rosindones) from quinone dichlorimine, *p*-nitroso-anilines, and *p*-nitroso-phenols with alkyl or aryl-β-naphthylamines (B. **29,** 2753; **34,** 940):


$ClN : C_6H_4 : NCl + C_6H_5NHC_{10}H_7$
$HN : C_6H_3$
N
$N(C_6H_5)$
$C_{10}H_6$
$HOC_6H_4NO + C_6H_5NHC_{10}H_7$
$O : C_6H_3$
N
$N(C_6H_5)$
$C_{10}H_6$.

(2) Indulines and indones result from the condensation of hydroxy-quinones and amino-quinones with phenylated *o*-diamines (B. **28,** 1714; A. **290,** 262):



Indones are formed when the indulines are heated with concentrated mineral acids or dilute alkalies.

The indulines are among the longest known aniline dyestuffs (Caro and Dale, 1865; Griess and Martius, 1866). Their constitution has been made more evident by a series of investigations prosecuted in recent years by Fischer and Heppe, Kehrmann, Nietzki, etc. (A. **272,** 306; **290,** 247; B. **29,** 1442, 2318, 2771).

The indulines are classified:

1. **Benzindulines,** $NH : C_6H_3(N_2C_6H_5)C_6H_4$, from phenazine.
2. (*a*) *iso***Rosindulines,** $NH : C_6H_3(N_2C_6H_5)C_{10}H_6$ } from naphtho-
   (*b*) **Rosindulines,** $NH : C_{10}H_5(N_2C_6H_5)C_6H_4$ } phenazine.
3. **Naphthindulines,** $NH : C_{10}H_5(N_2C_6H_5)C_{10}H_6$, from naphthazine.
4. **Flavindulines** (see above), which are derived from phenanthrophenazine and -naphthazine.

The ms-*alkyl* derivatives, corresponding to these *ms*-phenyl-compounds, have also been prepared in various ways (see B. **30,** 394, etc.).

The benzoindulines and *iso*rosindulines, on the one side, being derivatives of benzo-quinone, and the rosindulines and naphthindulines being derivatives of naphthoquinone, exhibit among themselves great similarity. The first two groups form violet to blue-coloured, sparingly soluble salts. Their application in calico printing depends upon their solubility in *acetin* (Vol. I.) (*acetin print*). The ros- and naphth-indulines are strong bases. Their salts have an intense red colour, and show red fluorescence. When their strongly acid solutions are diluted, a change in colour similar to that observed with the safranines occurs. The indulines, like the quinones, readily yield anilino-compounds upon digestion with anilines. Similarly, the indones, when heated with alkalies, become oxyindones. For the action of ammonia upon the indulins, see under Safranine.

Benzinduline, Aposafranine, $C_{18}H_{12}N_3$, results by deamination of phenosafranine. Further deamination yields the phenylphenazonium salt, which regenerates aposafranine by treatment with ammonia. Aposafranine, digested with aniline, forms **anilino-aposafranine** (B. **28,** 1709; **29,** 2967). Benzeneinduline is also obtained from *p*-amino-azobenzene and aniline. **Aminophenylbenzinduline,** $NH_2C_6H_4.N: C_6H_3(N_2C_6H_5)C_6H_4$, melting at 150°, is a side-product. By deamination it yields *phenylbenzinduline.* If *p*-amino-azo-benzene be heated with *p*-phenylene-diamine, a mixture of various amino-indulines is produced, and these form *paraphenylene blue,* a valued cotton dyestuff (A. **286,** 195).

*iso***Rosinduline,** $C_{10}H_6(N_2C_6H_5)C_6H_3 : NH$, from quinone dichlorimide and phenyl-β-naphthylamine, becomes phenylnaphthophenazonium (B. **29,** 2753) by deamination. Its *dimethyl* derivative is obtained from *p*-nitroso-dimethylaniline with aniline and α-naphthylamine. *Bâle Blue* (A. **272,** 311) is an anilino-derivative of this compound.

Rosinduline, $NH: C_{10}H_5(N_2C_6H_5)C_6H_4$, melting at 199°, is formed from benzene-azo-α-naphthylamine and aniline, from *o*-oxy-α-naphthoquinone-imide and *o*-amino-diphenylamine, as well as from 4-acetamino-*o*-naphtho-quinone and phenyl-*o*-phenylene-diamine. **ψ-Rosinduline,** an isomeride, is also produced by the last method. It differs from rosinduline in the position of the $N.C_6H_5$-group with reference to the naphthalene nucleus (B. **24,** 2167; A. **290,** 262).

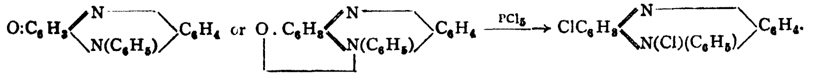
Rosinduline and *iso*rosinduline, by deamination, are converted into phenyl-naphtho-phenazonium salts, which regenerate rosinduline with ammonia.

Besides those mentioned, a whole series of isomeric rosindulines have been obtained by various methods (compare B. **31,** 3097; **32,** 2627; **33,** 1543, etc.).

Phenylrosinduline melts at 235°. *Azocarmine* is its disulphonic acid (D.R.P., 45,370).

Naphthinduline, $NH: C_{10}H_5(N_2C_6H_5)C_{10}H_6$, melts at 250°. It is obtained from benzene-azo-α-naphthylamine with naphthylamine and aniline (A. **262,** 262; **272,** 311). *Naphthyl violet* is its anilino-derivative. *Naphthyl blue* is the anilino-derivative of phenylnaphthinduline; it is produced by the inner condensation of benzene-azo-α-naphthyl-phenylamine.

Indones (A. **286,** 242).—By treatment with PCl_5 the indones yield chloro-phenazonium chlorides. Besides the *p*-quinone formula (see above), a phenol betaïne formula has therefore to be considered for these compounds (B. **33,** 1485; **41,** 12):



The indones combine with dimethyl sulphate to form methyl sulphates of methoxyphenazonium hydroxides (A. **322,** 73).

Apo-safranone, *benzolindone,* $C_{18}H_{12}N_2O$, m.p. 242°, is formed from apo-safranine bromide with NaHO (B. **33,** 1487). It gives with PCl_5 phenyl-chloro-phenazonium chloride (see above), and with hydroxylamine amino-apo-safranone, $C_{18}H_{11}N_2O(NH_2)$ (B. **38,** 3435).

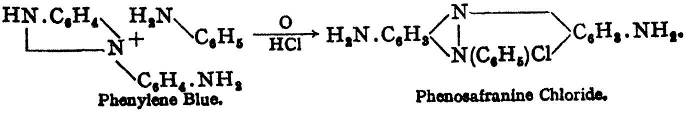
Rosindone, $O: C_{10}H_5(N_2C_6H_5)C_6H_4$, of the *indones* (see A. **286,** 242), occurs in the form of its sulphonic acid as a ponceau-red dyestuff having technical application.

With PCl_5 it yields phenyl-chloro-naphtho-phenazonium chloride, which with KSH gives thio-rosindone. With dimethyl sulphate rosindone yields **4-methoxy-naphtho-pheno-phenylazonium methyl sulphate,** $CH_3OC_{10}H_5(C_6H_5N_2.OSO_3CH_3)C_6H_4$. On the oxidation of rosindone with CrO_3 to the so-called rosindonic acid, see B. **36,** 3622.

*iso***Rosindone,** $C_{10}H_6(N_2C_6H_5)C_6H_3: O$, melting at 224°, is also obtained from nitroso-phenol and phenyl-β-naphthyl-amine (B. **29,** 2755). With PCl_5 it yields phenyl-naphtho-chloro-phenazonium chloride (B. **33,** 1494), and with hydroxylamine amino-*iso*-rosindone (B. **40,** 3406).

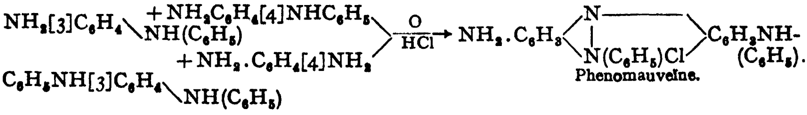
Naphthindone, $C_{10}H_5O(N_2.C_6H_5)C_{10}H_6$, m.p. 295°, with PCl_5 gives phenyl-chloro-naphthazonium chloride (B. **33,** 1497).

Safranines.—Safranine salts should be regarded as *symmetrical diamino-derivatives of the azonium salts.* They are produced (1) upon oxidizing a mixture of an indoamine and a monamine:

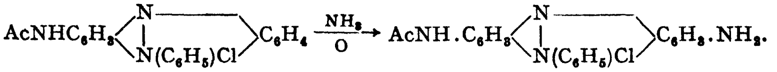


Phenylene Blue. Phenosafranine Chloride.

(2) By oxidizing a mixture of *m*-amino-derivatives of diphenylamine with *p*-diamines or quinone dichlorimides (B. **28,** 1579; **29,** 1444):



(3) By the action of ammonia upon the aceto-derivatives of certain indulines:



The safranines usually form monacid, red-coloured salts. The solutions in concentrated sulphuric or hydrochloric acids are green in colour. Upon dilution they become blue, then red (dissociation of unstable polyatomic salts; compare the eurhodines above). The reverse in colour-change occurs upon adding acid to the dilute salt solutions.

The sparing solubility of their nitrates is noteworthy. The alcoholic solutions usually exhibit a strong yellowish-red fluorescence. Views in regard to the structure of the free bases have been proposed. Reducing agents convert safranines into leuco-compounds, which in the presence of alkalies are rapidly reoxidized by the air to safranines.

The lowest member of the safranines is—

Phenosafranine, $C_{18}H_{15}N_4Cl$. It consists of leaflets, green in colour, or of steel-blue needles. Baryta separates *safranol.*

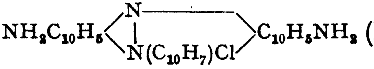
When its monodiazo-compound is boiled with alcohol, aposafranine chloride is produced; the acetyl derivative of the latter, upon treatment with ammonia, again yields an acetylphenosafranine (B. **30,** 1565). Unsymmetrical **dimethyl-** and **diethyl-phenosafranines** (B. **28,** 1356) are obtained from dimethyl- and diethyl-*p*-phenylenediamine with two molecules of aniline. Dimethylphenosafranine is the basis of the dyestuff *fuchsia.* The *Giroflé* of commerce is a homologue. *N*-**Tetraethylphenosafranine** is the violet dyestuff *amethyst.*

*iso***Phenosafranine,** $(NH_2)_2C_6H_2(N_2C_6H_5Cl)C_6H_4$, is obtained from dinitro-pheno-dihydro-phenazine (resulting from the condensation of picric acid with *o*-amino-diphenylamine) in the same way as are the corresponding compounds of the oxazine and thiazine series (B. **32,** 2608, 3155).

Tolusafranine, $C_{18}H_{13}(CH_3)_2N_4Cl$, from toluylenediamine *o*-toluidine (1 molecule) and aniline (1 molecule), is the chief constituent of common *safranine,* occurring in commerce as a brown paste or yellow-red powder, employed in cotton and silk dyeing as a substitute for safflor. The necessary base-mixture for its production is obtained from the "aniline oil for safranine." This is partially diazotized, and the product broken up into paratoluylenediamine and orthotoluidine by reduction.

Naphthophenosafranine Chloride, $NH_2C_{10}H_5(N_2C_6H_5.Cl)C_6H_3NH_2$. Its acetyl derivative is produced from acetylrosinduline and ammonia (B. **30,** 1566).

The dyestuff **indazine,** $C_6H_5NHC_6H_3(N_2ClC_6H_5)C_6H_3N(CH_3)_2$, is closely allied to the safranines in its method of formation. It melts at

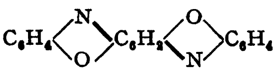
218°, and is obtained from diphenyl-*N*-phenylenediamine and nitrosodimethyl aniline. The analogous non-methylated body, from nitrosoaniline and diphenyl-*m*-phenylenediamine, or from *m*- and *p*-aminodiphenylamine, is identical with **Phenomauveine,** which is closely related to **mauveine,** the first aniline dye to prove valuable technically (Perkin, 1856). Mauveine is produced by oxidizing aniline containing toluidine with potassium bichromate or lead peroxide. **Magdala Red** belongs to the safranines (Hofmann, B. **2,** 412). It results from aminoazonaphthalene and α-naphthylamine hydrochloride. It probably has the following constitution:  $NH_2C_{10}H_5<\begin{matrix}N\\|\\N(C_{10}H_7)Cl\end{matrix}>C_{10}H_5NH_2$ (B. **26,** 2235 ; **30,** 1567).

Safraninones and **Safranols** are to be viewed as symmetrical amino- and oxyderivatives of the indones. Like the safranines, they are prepared from *m*-hydroxydiphenylamines with nitrosodimethyl aniline or nitrosophenol (B. **28,** 270, 503, 1354, 1578).

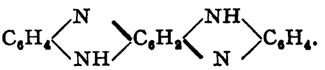
Safraninone, $C_{18}H_{13}N_3O$, and **Safranol,** $C_{18}H_{12}N_2O_2$, are made by boiling phenosafranine with baryta-water or caustic potash (B. **30,** 399).

With PCl_5, safranol gives *dichloro-phenazonium chloride,* ClC_6H_3-$(N_2.ClC_6H_5)C_6H_3Cl$ (B. **31,** 301).

Fluorindines.—Fluorindine is the simplest representative of this class of dyestuffs. It corresponds to triphenodioxazine:

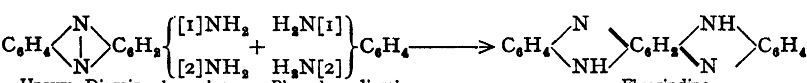


Triphenodioxazine.



Fluorindine.

The fluorindines result by oxidizing or heating the salts of *o*-diamines; unsymmetrical diaminophenazines appear as intermediate products:



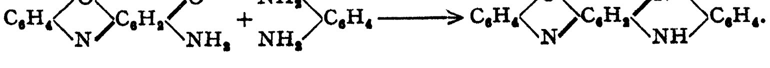
Unsym. Diaminophenazine. *o*-Phenylene-diamine. Fluorindine.

The fluorindines usually form green-coloured crystals, which sublime without decomposition and are sparingly soluble. Their solutions show a beautiful brick-red fluorescence.

***N*-Methylfluorindine,** $C_6H_4=(N_2H)=C_6H_2=(N_2CH_3)=C_6H_4$, is obtained from the hydrochloride of diamino-phenazine and methyl-*o*-phenylene-diamine (B. **28,** 395).

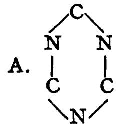
Phenylfluorindine, $C_6H_4N_2HC_6H_2N_2(C_6H_5)C_6H_4$, results from the condensation of aposafranine chloride with *o*-phenylene-diamine (B. **29,** 367). **Diphenylfluorindine,** $C_6H_4=(N_2C_6H_5)=C_6H_2=(N_2C_6H_5)=C_6H_4$, is produced in the oxidation of azophenine, and also from phenylinduline by sublimation (B. **28,** 293).

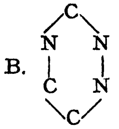
Triphenazineoxazine is a mixed oxazine-phenazine. It is formed from *unsym.* dihydroxyphenazine with *o*-aminophenol, or from aminophenoxazone with *o*-phenylene-diamine (B. **28,** 299):

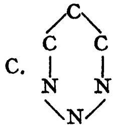


4. TRIAZINES.

Derivatives of the three possible metameric triazines are known:


Sym. Triazine, Cyanidine.

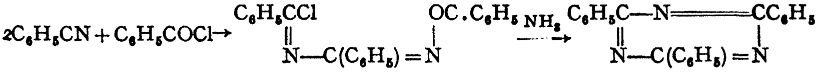

Unsym. (α)-Triazine.


v-(β)-Triazine.

A. *Symmetrical Triazines, Cyanidines.*—The formula of symmetrical triazine corresponds to the hypothetical *Trihydrocyanic Acid*, to which the metallo-hydrocyanic acids (Vol. I.) have been referred. Furthermore, a series of polymeric cyanogen compounds—*e.g.*, cyanuric acid, sulphocyanuric acid, cyanuric chloride, melamine, *iso*melamine, etc.—are derivatives of this triazine. They have already been discussed.

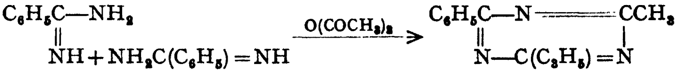
Alkyl- and *phenyl-derivatives* of symmetrical triazine or cyanidine are obtained:

1. By the action of aluminium chloride upon a mixture of benzonitrile and benzoyl chloride or acid chlorides. When benzoyl chloride is used, the reaction (best with the addition of ammonium chloride) proceeds as follows (B. **25**, 2263):



$$2C_6H_5CN + C_6H_5COCl \rightarrow \begin{array}{l} C_6H_5CCl \qquad\qquad OC.C_6H_5 \\ \| \qquad\qquad\qquad\quad | \\ N{-}C(C_6H_5){=}N \end{array} \xrightarrow{NH_3} \begin{array}{l} C_6H_5C{-}N{=}CC_6H_5 \\ \| \qquad\qquad\quad | \\ N{-}C(C_6H_5){=}N \end{array}$$

2. By the action of anhydrides of the fatty acids upon aromatic carbon-amidines (B. **25**, 1624):



$$\begin{array}{l} C_6H_5C{-}NH_2 \\ \| \\ NH + NH_2C(C_6H_5){=}NH \end{array} \xrightarrow{O(COCH_3)_2} \begin{array}{l} C_6H_5C{-}N{=}CCH_3 \\ \| \qquad\qquad | \\ N{-}C(C_3H_5){=}N \end{array}$$

Carbonyl chloride acts similarly to the anhydride of the fatty acid, with the production of oxycyanidines (B. **25**, 1424).

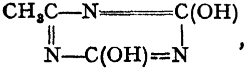
The cyanidines are weak monacid bases. They are more or less readily decomposed into ammonia and carbonic acids.

Diphenylmethylcyanidine, $C_3(C_6H_5)_2(CH_3)N_3$, melting at 110°, is made from benzamidine and acetic anhydride. It is oxidized to *diphenylcyanidinecarboxylic acid*, which loses water readily and becomes **diphenylcyanidine,** $C_3(C_6H_5)_2HN_3$, melting at 75° (B. **23**, 2382).

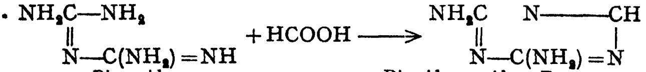
Triphenylcyanidine, Cyanphenine, $C_3(C_6H_5)_3N_3$, was first obtained from benzoyl chloride and potassium cyanate (Cloëz, 1859), then by the polymerization of benzonitrile with concentrated sulphuric acid; from benzonitrile, benzoyl chloride, and Al_2Cl_6 (see above), as well as by the action of sodium upon a mixture of cyanuric chloride and bromobenzene (proof of constitution). Compare B. **29**, R. 1124, for the action of sodium upon benzonitrile. Nascent hydrogen decomposes it into ammonia and lophine; compare the similar conversion of **Cyanurtriethyl,** *triethylcyanidine*, into triethylglyoxaline (B. **28**, R. 66). **Perchloro-trimethyl cyanidine,** $C_3(CCl_3)_3N_3$, melting at 96°, results from the polymerization of trichloracetonitrile.

Hexachlorotriethylcyanidine, $C_3(CCl_2.CH_3)_3N_3$, m.p. 74°, from propionitrile with chlorine, gives, with KSH, trithio-acetyl cyanidin, $C_3(CS.CH_3)_3N_3$ (J. pr. Ch. [2], **57**, 357).

Diphenylhydroxycyanidine, $C_3(C_6H_5)_2(OH)N_3$, melting at 289°, from benzenylamidine and $COCl_2$ (B. **23**, 163), forms a well-crystallizing sodium salt. PCl_5 converts it into *diphenylchlorocyanidine*, melting at 139°, which behaves like an acid chloride. Thus, ammonia readily changes it into *diphenylaminocyanidine*, melting at 172°.

Methyldihydroxycyanidine, 
$$\begin{array}{lcr} CH_3C{-}N & = & C(OH) \\ \| & & | \\ N{-}C(OH) & = & N \end{array}$$
, is obtained from acetyl urethane and urea (A. **288**, 318).

Amino-cyanidine, *amino-hydro-cyanuride*, $C_3H_2(NH_2)N_3$, and **Di-amino-cyanidine, diamino-cyanuride,** $C_3H(NH_2)N_3$, m.p. 325°, are formed by reducing cyanurimine dichloride and cyanurodiamine chloride respectively. The diaminocyanidine is identical with **formoguanamine** (B. **32**, 1219; see also Vol. I.). Guanamines in general are formed by heating aliphatic guanidine salts, or biguanide with fatty acids:

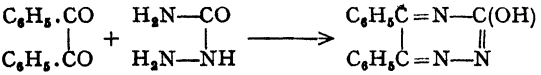

$$\begin{array}{l} NH_2C{-}NH_2 \\ \| \\ N{-}C(NH_2)=NH \end{array} + HCOOH \longrightarrow \begin{array}{l} NH_2C \quad N{-}CH \\ \| \qquad\quad | \\ N{-}C(NH_2)=N \end{array}$$

Biguanide. Diamido-cyanidine, Formo-guanamine.

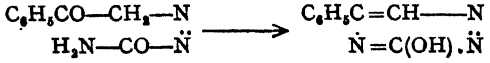
Piperylamino-cyanidine, $C_3(NC_5H_{10})(NH_2)HN_3$, melting at 194°, is similarly obtained by heating piperyl guanide with formic acid, or by treating it with chloroform and caustic potash, even at 0° (B. **25**, 525).

Normal cyanuric acid is a **trioxycyanidine,** cyanuric chloride is a **trichlorocyanidine,** melamine is **triaminocyanidine,** and ammelide and ammeline are **oxydiamino-** and **dioxyamino-cyanidines. Dimethoxy-** and **diethoxy-chlorocyanidines,** m.p. 81° and 44°, b.p.$_{13}$ 144°, are formed on treating cyanuric chloride with methyl and ethyl alcohol and zinc-dust. The former, with KSH, gives **dimethoxythiocyanidine,** which is saponified by HCl to **dihydroxythiocyanidine,** m.p. 316° with dec. (B. **36**, 3191). *iso*Cyanuric acid and its derivatives are to be regarded as derivatives of a triketo-hexahydro-cyanidine.

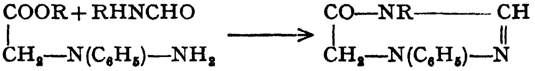
B. **Unsymmetrical** (α)-**Triazines.**—But few derivatives of the simple ring are known: 1,2-**Diphenyl-3-hydroxy-α-triazine,** $C_3(C_6H_5)_2(OH)N_3$, melting at 218°, is produced in the condensation of benzil with semicarbazide (B. **28**, R. 110):


$$\begin{array}{l} C_6H_5.CO \\ | \\ C_6H_5.CO \end{array} + \begin{array}{l} H_2N{-}CO \\ | \\ H_2N{-}NH \end{array} \longrightarrow \begin{array}{l} C_6H_5C=N{-}C(OH) \\ | \qquad\qquad \| \\ C_6H_5C=N{-}N \end{array}$$

Similarly, 1,2-**Diphenyl-3-amino-α-triazine,** $C_3(C_6H_5)_2(NH_2)N_3$, m.p. 175°, are obtained from benzil and aminoguanidine nitrate (A. **302**, 309). Some other triazines are derived from the phenacyl-azocyanide, $C_6H_5COCH_2N:NCN$; the amide, amido-chloride, and thiamide respectively pass on rejection of H_2O into **phenylhydroxy-, phenylchloro-,** and **phenylthio-α-triazine,** m.p. 234°, m.p. 123°, and m.p. 200° (B. **36**, 4126):

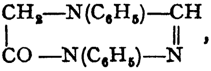

$$\begin{array}{l} C_6H_5CO{-}CH_2{-}N \\ H_2N{-}CO{-}\ddot{N} \end{array} \longrightarrow \begin{array}{l} C_6H_5C=CH{-}N \\ \dot{N}=C(OH).\dot{N} \end{array}$$

N-*Phenyl-* and N-*phenyl-*N-*alkyl-ketotetrahydro-a-triazines* are made by heating the unsymmetrical phenylhydrazino-acetic acid ester with formamide and substituted formamides (B. **28,** 1228):



$$\begin{array}{l}\mathrm{COOR+RHNCHO}\\ |\\ \mathrm{CH_2—N(C_6H_5)—NH_2}\end{array} \longrightarrow \begin{array}{lr}\mathrm{CO—NR—} & \mathrm{CH}\\ | & \|\\ \mathrm{CH_2—N(C_6H_5)—} & \mathrm{N}\end{array}$$

***N*-Diphenyl-keto-tetrahydro-triazine,** melting at 205°, is obtained from formanilide. An isomeric ***N*-diphenylketo-tetrahydro-triazine,**



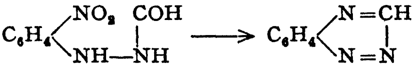
$$\begin{array}{lr}\mathrm{CH_2—N(C_6H_5)—} & \mathrm{CH}\\ | & \|\\ \mathrm{CO—N(C_6H_5)—} & \mathrm{N}\end{array}$$

, melting at 174°, has been prepared from anilino-acetic acid phenylhydrazide, $C_6H_5NHCH_2CON(C_6H_5)NH_2$, with crystallized formic acid (B. **26,** 2616).

***N*-Diphenyl-diketo-hexahydro-*a*-triazine,** m.p. 258°, is formed from unsymmetrical phenyl-hydrazino-acetanilide with phosgene (A. **301,** 69).

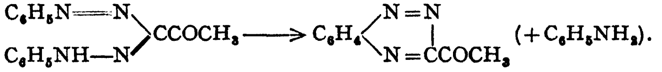
1-Methyl-2,3-diketo-hexahydro-*a*-triazine,$C_3(CH_3)O_2H_4N_3$,m.p. 214°, from semi-carbazido-propionic acid nitrile, $NH_2CONH.NHCH(CH_3)CN$, with concentrated HCl, is converted by bromine into **methyl-dihydroxy-*a*-triazine,** m.p. 209°, which contains two H-atoms less (A. **303,** 76).

The derivatives of *benzo-* or *pheno-a-triazine* are more numerous. They are produced (1) by the reduction of symmetrical *o*-nitrophenyl-acidyl hydrazines:



$$\mathrm{C_6H_4}\left\langle\begin{array}{ll}\mathrm{NO_2} & \mathrm{COH}\\ & |\\ \mathrm{NH—} & \mathrm{NH}\end{array}\right. \longrightarrow \mathrm{C_6H_4}\left\langle\begin{array}{ll}\mathrm{N=} & \mathrm{CH}\\ & |\\ \mathrm{N=} & \mathrm{N}\end{array}\right.$$

(2) By the condensation of formazyl compounds on boiling them with concentrated acids (B. **25,** 3206, 3540; **26,** 2788):

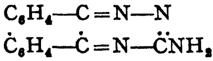


$$\left.\begin{array}{l}\mathrm{C_6H_5N{=\!=}N}\\ \mathrm{C_6H_5NH—N}\end{array}\right\rangle\mathrm{CCOCH_3} \longrightarrow \mathrm{C_6H_4}\left\langle\begin{array}{ll}\mathrm{N=} & \mathrm{N}\\ & |\\ \mathrm{N=} & \mathrm{CCOCH_3}\end{array}\right. \quad (+\mathrm{C_6H_5NH_2}).$$

The pheno-*a*-triazines are *yellow*-coloured, crystalline compounds, having an alkaloid-like odour. They are very slightly basic.

Phenotriazine, $C_6H_4(CN_3H)$, melting at 75° and boiling at 235°–240°, results from the reduction of *o*-nitrophenylformylhydrazine, or by the exit of CO_2 and aniline from formazyl carboxylic ester. **Methyl-phenotriazine,** $C_6H_4[CN_3(CH_3)]$ melting at 89° and boiling at 250° to 255°, is obtained from *o*-nitrophenylacetylhydrazine. **Pheno-triazyl methyl ketone,** $C_6H_4[CN_3(COCH_3)]$, melting at 114°, is derived from formazyl methyl ketone.

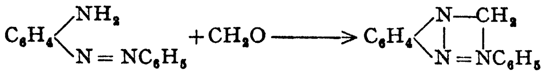
Aminophenanthrotriazine,



$$\begin{array}{l}\mathrm{C_6H_4—C=N—N}\\ \quad\ \ \vdots\qquad\qquad\ \vdots\\ \mathrm{C_6H_4—C=N—CNH_2}\end{array}$$

, m.p. 262°, and **hydroxyphenanthrotriazine,** m.p. 285° with dec., from phenanthrene quinone with amino-guanidine nitrate and semicarbazide hydrochloride respectively (A. **302,** 310; B. **44,** 276).

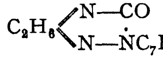
The *phenodihydro-a-triazines* are related to the pheno-*a*-triazines. They are obtained, instead of the expected alkylidene amino-derivatives (B. **24,** 1002, R. 948), from *o*-amino-azo-compounds and aldehydes:



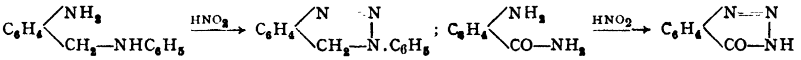
$$C_6H_4{<}\begin{matrix}NH_2\\N=NC_6H_5\end{matrix}+CH_2O\longrightarrow C_6H_4{<}\begin{matrix}N-CH_2\\|\qquad|\\N=NC_6H_5\end{matrix}$$

These compounds are *colourless.* They are feebly basic, stable bodies, which can be heated with hydrochloric acid to 150° without decomposition.

N-**Tolyl-tolu-α-dihydro-triazine,** $C_7H_6[CH_2N_3(C_7H_7)]$, melts at 178°. *N*,*C*-**diphenyl-aminopheno-α-dihydro-triazine,** $NH_2C_6H_3[CH(C_6H_5)_2N_3]$, m.p. 223°, from chrysoïdine and benzaldehyde (B. **30,** 2595). *N*,*C*-**Diphenyl-naphtho-α-dihydro-triazine,** $C_{10}H_6[CHN_3(C_6H_5)_2]$, melting at 193°, is formed from benzene azo-β-naphthylamine and benzaldehyde.

N-**Tolyl-tolu-dihydro-α-triazone,**  $C_2H_6{<}\begin{matrix}N-CO\\|\\N-NC_7H_7\end{matrix}$, m.p. 168°, from *o*-aminoazotolene with $COCl_2$, is not changed by boiling with HCl, but is easily broken up by bases. *N*-**Phenylnaphtho-dihydro-triazone,** m.p. 255°, is also formed from the urethane of benzene-azo-β-naphthylamine with alcoholic potash. The anilino-derivatives of the pheno-dihydro-triazins are obtained by withdrawing SH_2 from the phenyl mustard oil addition products of the *o*-amino-azo-compounds (B. **32,** 2959).

C. *Phenodihydro-β-triazines* are derived from adjacent *v*- or β-**Triazine.** They are ring homologues of the azimino-benzenes, and are prepared from the *o*-aminobenzylamines and *o*-aminobenzamides with nitrous acid, just as the pheno-dihydro-meta-diazines or dihydro-quinazolines are obtained from the carboxylic acids:



$$C_6H_4{<}\begin{matrix}NH_2\\CH_2-NHC_6H_5\end{matrix}\xrightarrow{HNO_2}C_6H_4{<}\begin{matrix}N\quad N\\\qquad|\\CH_2-N.C_6H_5\end{matrix};\ C_6H_4{<}\begin{matrix}NH_2\\CO-NH_2\end{matrix}\xrightarrow{HNO_2}C_6H_4{<}\begin{matrix}N=N\\\quad|\\CO-NH\end{matrix}$$

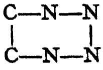
N-**Phenylphenodihydro-β-triazine,** $C_6H_4[CH_2N_3(C_6H_5)]$, melts with decomposition at 128° (B. **25,** 445).

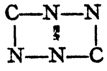
N-**Benzylphenodihydro-β-triazine,** $C_6H_4[CH_2N_3(C_7H_7)]$, melts at 91° (B. **28,** R. 383).

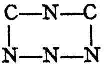
Pheno-ketodihydro-β-triazine, *Benzazimide,* $C_6H_4[CON_3H]$, melts with decomposition at 212°. It is obtained from *o*-amino-benzamide with nitrous acid, or from *Iz*-amido-indazol by oxidation with H_2O_2 in acid solution; its oxime results from *o*-amino-benzenyl amidoxime with N_2O_3 (J. pr. Ch. [2] **37,** 432; **43,** 446; **48,** 92; B. **29,** 626, R. 785). **Thiobenzazimide,** $C_6H_4[CSN_3H]$, m.p. 187°, from *o*-amino-thio-benzamide with NO_2H (B. **42,** 3719). *N*-**Phenyl-benzazimide,** $C_6H_4[CON_3C_6H_5]$, m.p. 151°, from *o*-amino-benzanilide with N_2O_3 (B. **32,** 784); also from diazoaminobenzene-*o*-carboxylic ester on boiling with alcohol (J. pr. Ch. [2], **64,** 70).

5. TETRAZINES.

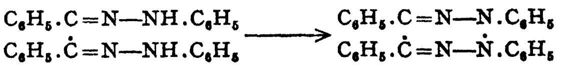
Only the first two of the three possible metameric tetrazine rings are known in certain derivatives:

A.  $\begin{array}{c}C-N-N\\|\qquad\quad|\\C-N-N\end{array}$

B.  $\begin{array}{c}C-N-N\\|\qquad\quad|\\N-N-C\end{array}$

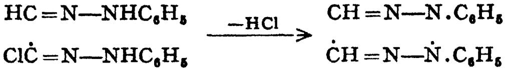
C.  $\begin{array}{c}C-N-C\\|\qquad\quad|\\N-N-N\end{array}$

A. *Osotetrazines* are derived from adjacent or *v*-tetrazines, and must be regarded as N-dihydro-*v*-tetrazines. They are derived from the osazones by oxidation:



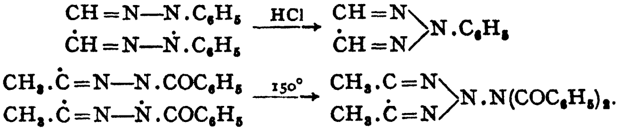
$$\begin{array}{l} C_6H_5.C=N-NH.C_6H_5 \\ C_6H_5.\dot{C}=N-NH.C_6H_5 \end{array} \longrightarrow \begin{array}{l} C_6H_5.C=N-N.C_6H_5 \\ C_6H_5.\dot{C}=N-\dot{N}.C_6H_5 \end{array}$$

Chloro-glyoxal-osazone and its homologues, treated with alkali, split off HCl and give diphenyl-osotetrazines (B. **38,** 2986):



$$\begin{array}{l} HC=N-NHC_6H_5 \\ Cl\dot{C}=N-NHC_6H_5 \end{array} \xrightarrow{-HCl} \begin{array}{l} CH=N-N.C_6H_5 \\ \dot{C}H=N-\dot{N}.C_6H_5 \end{array}$$

On heating alone or with mineral acids the osotetrazines become osotriazoles (B. **42,** 659):

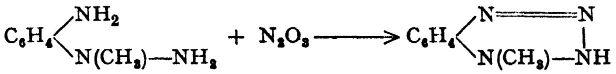


$$\begin{array}{l} CH=N-N.C_6H_5 \\ \dot{C}H=N-\dot{N}.C_6H_5 \end{array} \xrightarrow{HCl} \left.\begin{array}{l} CH=N \\ \dot{C}H=N \end{array}\right\rangle N.C_6H_5$$

$$\begin{array}{l} CH_3.\dot{C}=N-N.COC_6H_5 \\ CH_3.\dot{C}=N-\dot{N}.COC_6H_5 \end{array} \xrightarrow{150^\circ} \left.\begin{array}{l} CH_3.C=N \\ CH_3.\dot{C}=N \end{array}\right\rangle N.N(COC_6H_5)_2.$$

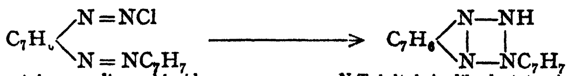
N-**Diphenylosotetrazine,** *glyoxal-osotetrazine,* dark red flakes, m.p. 152°. *C*-**Dimethyl-***N***-dibenzoyl-osotetrazine,** colourless needles, m.p. 140°.

N-**Methylbenzodihydrotetrazine,** melting at 62°, is a *benzo-derivative* of *v*-tetrazine. It is formed when nitrous acid acts upon *o*-amino-phenylmethylhydrazine, and corresponds to the phenyl-dihydro-*β*-triazines (J. pr. Ch. [2], **41,** 176):



$$C_6H_4\left\langle\begin{array}{l} NH_2 \\ N(CH_3)-NH_2 \end{array}\right. + N_2O_3 \longrightarrow C_6H_4\left\langle\begin{array}{l} N=\!=\!=\!=N \\ N(CH_3)-NH \end{array}\right.$$

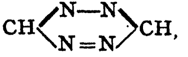
The iso*phendihydrotetrazines,* on the other hand, are constituted analogously to the phenyldihydro-*α*-triazines. They result by the reduction of the diazo-salts of *o*-amino-azo-compounds (II. 144) (B. **19,** 1457; **21,** 543):



$$C_7H_6\left\langle\begin{array}{l} N=NCl \\ N=NC_7H_7 \end{array}\right. \longrightarrow C_7H_6\left\langle\begin{array}{l} N-NH \\ N-NC_7H_7 \end{array}\right.$$

Azotoluene-*o*-diazo-chloride. *N*-Tolyltolu*iso*dihydrotetrazine, m.p. 168°.

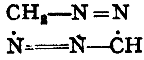
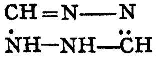
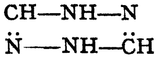
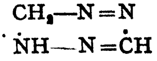
B. The symmetrical tetrazines are obtained by the oxidation of their dihydro-compounds, and are distinguished by their intensely red colour.

Symmetrical **Tetrazine,**  $CH\left\langle\begin{array}{c} N-N \\ N=N \end{array}\right\rangle CH$, purple columns, subliming without decomposition at 99°, is formed by heating its dicarboxylic acid (see below). SH_2 reduces it with decoloration to dihydrotetrazine, from which it is easily regenerated by oxidation (B. **40,** 84).

Symmetrical **Diphenyltetrazine,** $C_2(C_6H_5)_2N_4$, red leaflets, m.p. 192°, by oxidation of N,*v*-dihydro-*C*-diphenyltetrazine (B. **27,** 984, 3273).

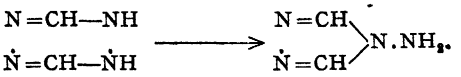
Symmetrical **Tetrazine dicarboxylic acid,** $C_2(CO_2H)_2N_4$, carmine-coloured leaflets, is formed by the oxidation of bis-diazo-acetic acid and pseudo-diazo-acetic acid or its amide with nitrous acid or bromine. On heating with water it splits up into N_2 and *glyoxal-hydrazin oxalic acid,* $CO_2H.CH:N.NH.CO.CO_2H$ (B. **40,** 1176).

Symmetrical Dihydro-tetrazines.—Four isomers are possible:

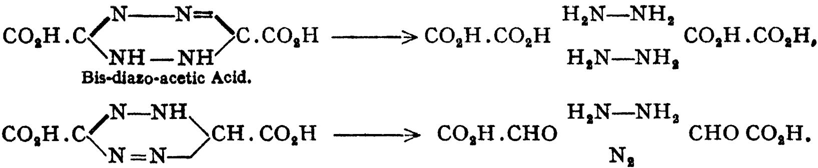
I.  II.  III.  IV. 

known as *C*-**Dihydrotetrazine,** *N,v*-**Dihydrotetrazine,** *N,s*-**Dihydrotetrazine,** and *C,N*-**Dihydrotetrazine** respectively.

By oxidation the N,*v*-dihydro-tetrazines easily pass into the corresponding tetrazines, from which they are also obtained by reduction. We may note the easy transformation of the N,*v*-dihydrotetrazines into *N*-aminotriazoles:

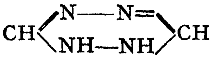


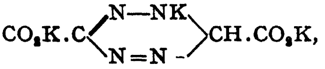
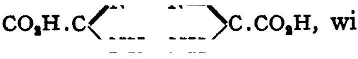
On heating with water or dilute acids the dihydrotetrazines are split up. The hydrolysis always takes place in such a manner that two nitrogen atoms, singly linked to each other, form hydrazine, and two doubly-linked N-atoms form free nitrogen:



Bis-diazo-acetic Acid.

Pseudo-diazo-acetic Acid.

N,v-**Dihydrotetrazine,**  light yellow prisms, m.p. 126°, is formed by the reduction of tetrazine with SH_2. On fusion it transposes into *N*-aminotriazole (see above). Mineral acids split it up into hydrazine and formic acid (B. **40,** 821).

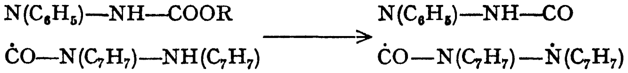
The foundation substances for the preparation of the simplest tetrazine and dihydrotetrazine derivatives are the polymerization products of diazo-acetic ester (B. **41,** 3161). Treatment of diazo-acetic ester with *cold* concentrated KHO produces the tri-potassium salt of *C,N*-**dihydrotetrazine dicarboxylic acid,** pseudo-*diazoacetic acid,*  from which the free acid has not yet been isolated. On heating with concentrated alkalies, *pseudo*-diazoacetic acid is transposed into *N,v*-**Dihydrotetrazinedicarboxylic acid,** *Bis-diazoacetic acid,*  with displacement of an H-atom. This body can also be obtained direct by the action of concentrated hot alkalies upon diazoacetic ester. Prolonged heating with highly concentrated KHO converts *iso*diazoacetic acid into a mixture of *N*-aminotriazole dicarboxylic acid and *C*-aminotriazole monocarboxylic acid. On fusion, *iso*diazoacetic acid splits up into CO_2 and dihydrotetrazine, which immediately transposes into *N*-aminotriazole.

N,v-**Dihydro-*C*-diphenyltetrazine,** consisting of yellow needles, m.p. 204°. This is produced by the action of excess of hydrazine upon benzimido-ether.

The dihydro-derivative is converted into tetrazine by heating, by moderated oxidants, and even by the oxygen of the air. It can be regained from the tetrazine by reducing the latter with zinc dust and glacial acetic acid. If the body be boiled with these reagents, the reduction extends further: ammonia and *diphenyltriazole* are produced. When dihydrodiphenyltetrazine is boiled with hydrochloric acid, it forms in part *diphenyloxydiazole* (p. 138) and in part it becomes the isomeric *N*-aminodiphenyltriazole.

N,c-**Tetraphenyl-s-dihydro-tetrazine,** $C_2N_4(C_6H_5)_4$, yellow needles, m.p. 204°, is formed from phenyl-nitro-formaldehydrazone with Na methylate. Also from benzaldehyde-phenyl-hydrazone or dihydrobenzal-phenyl-hydrazone with Na alcoholate and iodine (B. **34**, 523).

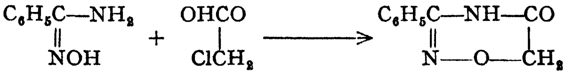
N-**Tetraphenyl-hexahydro-tetrazine,** $(C_6H_5)_2N_2(CH_2)_2N_2(C_6H_5)_2$, m.p. 200°, from hydrazobenzene and formaldehyde (B. **31**, 3250; J. pr. Ch. [2], **65**, 97). A derivative of hexahydro-tetrazine is formed from phenyl-dibenzyl-carbazide carboxylic ester with alcoholic potash (B. **34**, 2311):



$$\begin{array}{l} N(C_6H_5)—NH—COOR \\ \dot{C}O—N(C_7H_7)—NH(C_7H_7) \end{array} \longrightarrow \begin{array}{l} N(C_6H_5)—NH—CO \\ \dot{C}O—N(C_7H_7)—\dot{N}(C_7H_7) \end{array}$$

6. *Substances consisting of polyhetero-atomic six-membered rings, which contain* O- *and* S-*members, in addition to nitrogen, are not very numerous.* Some are produced in reactions similar to those in which the corresponding five-membered rings are formed.

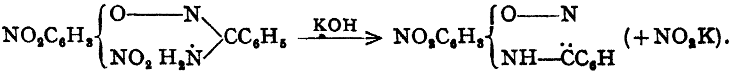
Just as the five-membered azoximes are prepared from the amidoximes and carboxylic acid chlorides, so their corresponding six-membered ring homologues are prepared from amidoximes and α-chloro-fatty acids (B. **22**, 3161; **27**, 3353; **28**, 1374; **29**, 2656; **31**, 2110):



$$\begin{array}{c} C_6H_5C—NH_2 \\ \| \\ NOH \end{array} + \begin{array}{c} OHCO \\ | \\ ClCH_2 \end{array} \longrightarrow \begin{array}{l} C_6H_5C—NH—CO \\ \;\;\;\| \qquad\qquad\;\; | \\ \;\;N——O——CH_2 \end{array}$$

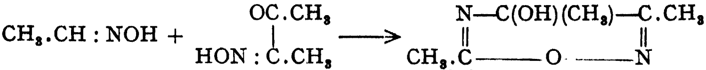
Benzenylamidoxime. **Chloracetic Acid.** **Benzenylamidoxime-acetic Acid Isoanhydride, m.p. 148°.**

Benzo-derivatives of this ring are formed from the dinitrophenol ethers of amidoximes by means of alkalies with a loss of an NO_2-group:



$$NO_2C_6H_3\left\{\begin{array}{l} O——N \\ NO_2\;H_2N \end{array}\right. \!\!\!\!> CC_6H_5 \xrightarrow{KOH} NO_2C_6H_3\left\{\begin{array}{l} O——N \\ NH—\ddot{C}C_6H \end{array}\right. (+NO_2K).$$

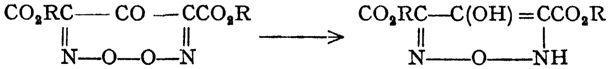
The so-called *oxo-diazines*, formed by the condensation of *iso*-nitroso-ketones with aldoximes, are regarded as homologues of the azoximes (B. **40**, 4052):



$$CH_3.CH:NOH + \begin{array}{l}OC.CH_3\\ \;|\\ HON:C.CH_3\end{array} \longrightarrow \begin{array}{lcr}N—C(OH)(CH_3)—C.CH_3 & & \\ \| \qquad\qquad\qquad\quad \| & & \\ CH_3.C——O——N & & \end{array}$$

Hydroxytrimethyloxydiazine.

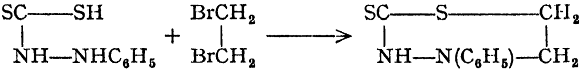
The five-membered furazans or azoxazoles have corresponding six-membered *azoxazine* derivatives. The reduction of di-*iso*-nitroso-acetone dicarboxylic ester peroxide leads to **oxy-azoxazine dicarboxylic ester**:



$$\begin{array}{l}CO_2RC—CO—CCO_2R\\ \|\qquad\qquad\qquad \|\\ N—O—O—N\end{array} \longrightarrow \begin{array}{l}CO_2RC—C(OH)=CCO_2R\\ \|\qquad\qquad\qquad |\\ N——O——NH\end{array}$$

from which a series of additional azoxazine compounds has been prepared (B. **26**, 999).

The *thiodiazines* or *diazothines* are homologues of the thio-[b,b_1]-diazoles. An *N*-**phenyl-tetrahydrothiodiazinethione,** melting at 94°, is formed in the condensation of phenylsulpho-carbazinic acid with ethylene bromide (B. **27**, 2516):



$$\begin{array}{l}SC——SH\\ |\\ NH—NHC_6H_5\end{array} + \begin{array}{l}BrCH_2\\ |\\ BrCH_2\end{array} \longrightarrow \begin{array}{l}SC——S————CH_2\\ |\qquad\qquad\qquad\quad |\\ NH—N(C_6H_5)—CH_2\end{array}$$

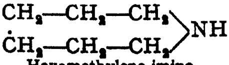
N-**Phenyl-*C*-amino-keto-dihydro-thiodiazine,** *Phenyl-amino-pyrithiazinone,* $\frac{OC.CH_2.S}{C_6H_5\dot{N}.N:\dot{C}(NH_2)}$, m.p. 176°, is formed by condensation of sulpho-cyano-acetic acid with phenyl-hydrazine (B. **33**, 1154).

A six-membered ring with two S-members and one N-member is contained in the thialdines (see Vol. I.), obtained from the tri-thio-aldehydes by the action of ammonia.

7. SEVEN, EIGHT-, AND MANY-MEMBERED HETEROCYCLIC SUBSTANCES.

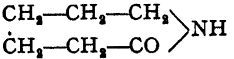
The tendency to form hetero-rings with more than six ring members is, as already mentioned, rare, as in the carboxylic compounds. Yet the variety of conditions which may give rise to hetero-rings enables, in some cases, hetero-rings of seven, eight, or more members to be formed. A systematic treatment of these only partly investigated substances is at present impracticable. A summary of compounds of this class is therefore here appended.

1. SEVEN-MEMBERED HETERO-RINGS.



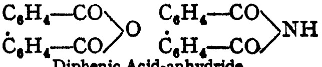
$$\left.\begin{array}{l}CH_2—CH_2—CH_2\\ \dot{C}H_2—CH_2—CH_2\end{array}\right\rangle NH$$

Hexamethylene-imine (B. **38**, 3091).



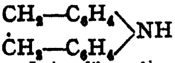
$$\left.\begin{array}{l}CH_2—CH_2—CH_2\\ \dot{C}H_2—CH_2—CO\end{array}\right\rangle NH$$

ε-Caprolactam (s. Bd. I).

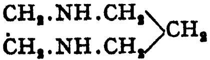


$$\left.\begin{array}{l}C_6H_4—CO\\ \dot{C}_6H_4—CO\end{array}\right\rangle O \qquad \left.\begin{array}{l}C_6H_4—CO\\ \dot{C}_6H_4—CO\end{array}\right\rangle NH$$

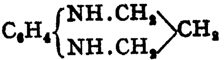
Diphenic Acid-anhydride and -imide (S. 537).



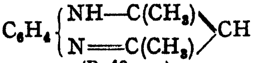
Imino-dibenzyl (A. **305**, 100)



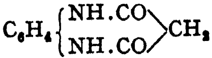
Ethylene-trimethylene-diamine (B. **32**, 2041).



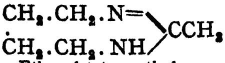
o-Phenylene-trimethylene-diamine (A. **287**, 220).



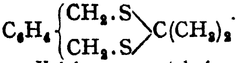
(B. **40**, 955).



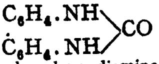
o-Phenylenemalonamide (A. **327**, 26).



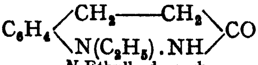
Ethenyl-tetramethylene-amidine (B. **36**, 338).



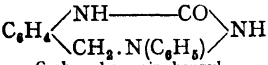
o-Xylylene-mercaptal of Acetone (B. **34**, 1775).



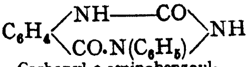
Carbonyl-*o*,*o*-diamino-diphenyl (B. **34**, 3330).



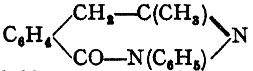
N-Ethylhydrocarb-azo-styril. (A. **301**, 282).



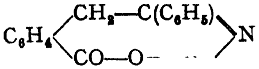
Carbonyl-*o*-aminobenzyl-phenyl-hydrazine (B. **27**, 2897).



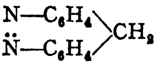
Carbonyl-*o*-aminobenzoyl-phenyl-hydrazine (A. **301**, 93).



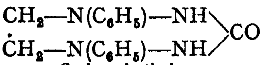
Methyl-benzylketone-*o*-carboxylic acid phenyl-lactazam (B. **32**, 966).



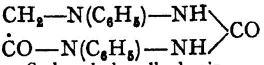
Desoxybenzoïn-*o*-carboxylic acid lactazone (B. **18**, 2449).



Azo-diphenyl-methane (C. 1903 I. 1416).

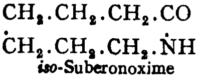


Carbonyl-ethylene Diphenyl-hydrazine (A. **310**, 156).



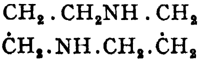
Carbonyl-phenylhydrazino-aceto-phenyl-hydrazide (A. **310**, 87).

2. EIGHT-MEMBERED HETERO-RINGS.



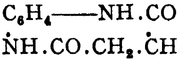
$$\begin{array}{l}CH_2.CH_2.CH_2.CO\\ \dot{C}H_2.CH_2.CH_2.\dot{N}H\end{array}$$

iso-Suberonoxime (Vol. I.).



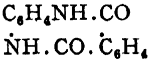
$$\begin{array}{l}CH_2\,.\,CH_2NH\,.\,CH_2\\ \dot{C}H_2.NH.CH_2.\dot{C}H_2\end{array}$$

Bistrimethylene-diamine (B. **32**, 2038).



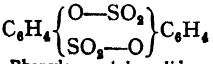
$$\begin{array}{l}C_6H_4\text{——}NH.CO\\ \dot{N}H.CO.CH_2.\dot{C}H_2\end{array}$$

o-Phenylene-succin-amide (A. **327**, 21).

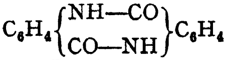


$$\begin{array}{l}C_6H_4NH.CO\\ \dot{N}H.CO.\dot{C}_6H_4\end{array}$$

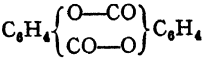
o-Phenylene-phthal-amide (A. **327**, 41).



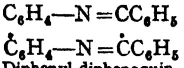
Phenylene-sulphonylide.



Dianthranilide.

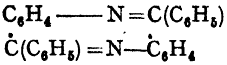


Disalicylide.

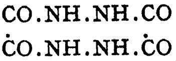


$$\begin{array}{l}C_6H_4\text{—}N=CC_6H_5\\ \dot{C}_6H_4\text{—}N=\dot{C}C_6H_5\end{array}$$

[Diphenyl-diphenoquin-oxalin (B. **26**, 1704).



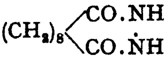
$$\begin{array}{l}C_6H_4\text{——}N=C(C_6H_5)\\ \dot{C}(C_6H_5)=N\text{—}\dot{C}_6H_4\end{array}$$



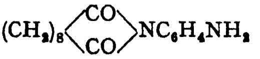
$$\begin{array}{l}CO.NH.NH.CO\\ \dot{C}O.NH.NH.\dot{C}O\end{array}$$

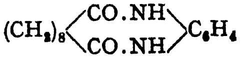
Dioxalyldihydrazide (?) (J. pr. Ch. [2], **52**, 223).

3. MANY-MEMBERED HETERO-RINGS.

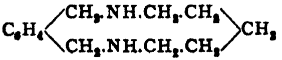


Sym. Sebacic acid hydrazide (Vol. I).

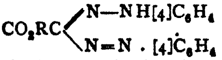




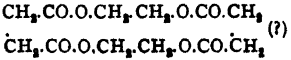
o-Amidoanil and *o*-Phenylenediamide of sebacic acid (A. **327**, 13).



o-Xylylenepentamethylene diamine (B. **31**, 1700).



Cycloformazylcarboxylic acid ester.



$$\begin{array}{l}CH_2.CO.O.CH_2.CH_2.O.CO.CH_2\\ \dot{C}H_2.CO.O.CH_2.CH_2.O.CO.\dot{C}H_2\end{array}\ (?)$$

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